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SEGMENTAL PNEUMONECTOMY IN BRONCHIECTASIS

THE LINGULA SEGMENT OF THE LEFT UPPER LOBE

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A NEW chapter in surgical anatomy dedicated to the detailed structure of the lung has been opened by the operative surgery of bronchiectasis and a more precise study of the pathology of that disease. Solely as a concession to operative technics, the lobe has been considered the surgical unit of the lung. The very name of the operation of lobectomy indicates the general acceptance of this concept.

A lobe is merely a segment of lung bounded by more or less constant and complete external fissures. It has been the convenience of these fissures rather than the underlying pathology that has defined the areas for pulmonary resection. A lobe of the lung, however, is in reality made up of a cluster of bronchopulmonary segments.

Greater precision in diagnosis and operative technic now indicates that the bronchopulmonary segment may replace the lobe as the surgical unit of the lung. This concept is developed in presenting the diagnostic and surgical aspects of the lingula segment of the left upper lobe. The basic principles of the concept, however, transcend the importance of this one bronchopulmonary segment and their wider application will be referred to briefly.

Bronchiectasis is frequently limited to one or more bronchopulmonary segments within a lobe, the remainder of the lobe being normal. It also tends to be primarily multilobar in its distribution. In a series of 86 cases of bronchiectasis operated upon by one of the authors (E. D. C.) at the Massachusetts General Hospital, the disease was limited to the confines of a single lobe in only 20 per cent. This characteristic of the disease provides a rational basis for proposing the resection of diseased bronchopulmonary segments from several lobes, if necessary, with the conservation of normal lung segments, rather than continuing with the removal of entire lobes as unit structures. This principle finds particular application in early cases of bronchiectasis and those with a bilateral distribution.

An accurate appraisal of the extent and distribution of bronchiectatic

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areas requires precision in the technic and interpretation of lipiodol bronchography and insistence upon complete visualization of not only the main bronchi but of every secondary and tertiary branch bronchus as far as its finer ramifications. Such detailed study is essential in nearly every case if a practical working basis is to be established for eradication of the disease by surgical methods.

Satisfactory surgical results in bronchiectasis can be achieved by the removal of all diseased segments of lung tissue, but the removal of a single lobe in a case of multilobar disease can lead only to disappointment unless the operation is undertaken as a palliative rather than a curative measure. A failure to delineate the complete pattern of the disease before the operation is the first step toward unsatisfactory operative results.

In our experience, bronchiectasis usually has reached its full extent and distribution at the time the diagnosis is made. The concept that bronchiectasis spreads insidiously from lobe to lobe has received undeserved support from the fortuitous demonstration of dilated bronchi by incomplete bronchograms in varying portions of the lung at different examinations. In rare instances a spread of bronchiectasis has been observed, usually as a sequel to an acute pneumonitic episode. In general, however, the anatomic pattern of the disease remains static over long periods of time although the symptoms are notoriously subject to variation. Any attempt to explain an unsatisfactory surgical result on the basis of postoperative extension of the disease appears contrary to the observed facts of preoperative pathology.

A recent survey of the Massachusetts General Hospital cases revealed that the lingula is also involved sufficiently to demand resection in at least 80 per cent of the cases of bronchiectasis of the left lower lobe, the most common site of the disease. The disappointing clinical results of some lobectomies can be explained by the failure to appreciate this high incidence and the perpetuation of cough and sputum attributed to residual disease in an unresected lingula. The lingula process of the left upper lobe stands, therefore, as an anatomic entity of great practical significance.

The Surface Anatomy of the Lingula.—It has been suggested by Nelson[8] that each lung is normally composed of four lobes: Upper, middle, lower and dorsal.* The evidence presented in support of this suggestion depends upon:

* The "dorsal lobe" is the synonym for the apical portion of the lower lobe. It is supplied by the first dorsal branch of the lower lobe stem bronchus, arising opposite the middle lobe bronchus on the right, and 1 to 2 cm. below the upper lobe bronchus on the left. The artery to the dorsal lobe arises from the inferior of the two main divisions of the pulmonary artery, close to its origin, and passes downward and medially, posterior to the main stem bronchus. The vein from the dorsal lobe drains into the inferior pulmonary vein (Fig. 5). Well developed fissures between the dorsal lobe and lower lobe proper are seen occasionally, and not infrequently the plane of cleavage is indicated by an incomplete horizontal fissure at the level of, or below, the fissure between the middle lobe and the upper lobe. This fissure is seen more commonly on the right side than on the left, especially in the lungs of children. Dévé[3] records a well defined fissure in 20 out of 180 lungs examined. Levitin and Brunn[7] have also described the two major bronchovascular segments that make up the lower lobe, with particular emphasis on the embryology and roentgenologic appearance.

(1) The demonstration by dissection of four major bronchovascular segments in each lung; and (2) the not infrequent occurrence of rudimentary fissures, constant in position but not in degree of development, subdividing the lung into four lobes. Each lobe possesses an independent bronchus and blood supply and is separated from the adjacent lobes by either a complete or partial fissure, or by an avascular plane of cleavage across which no vascular communications are encountered until the hilum is approached.

For descriptive purposes, the lingula process may be considered as the homologue of the right middle lobe, although embryologists are not unanimous in accepting this designation. It occupies a corresponding position; but, whereas, the fissure between the right upper and middle lobes is usually well developed, this is uncommon on the left side.

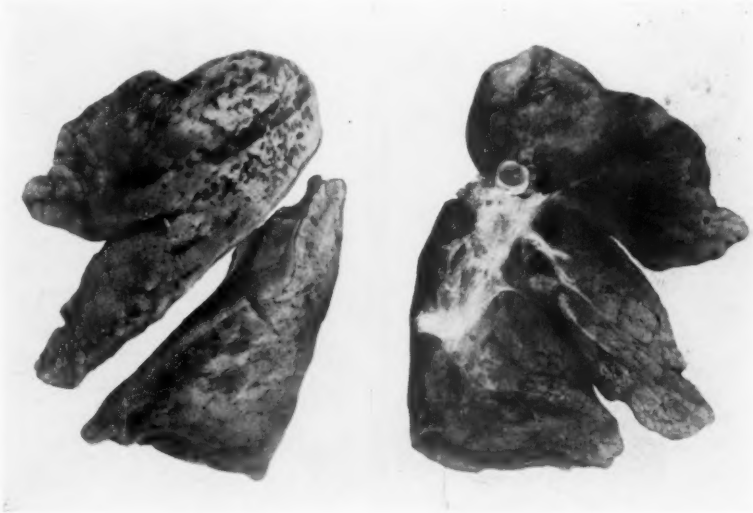

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FIG. 1.—Normal human left lung showing well developed fissure between the upper lobe and the lingula.

Figure 1 demonstrates a left lung in which the fissure between the upper lobe and lingula is well developed except posteriorly; a rudimentary dorsal lobe fissure is also present in this specimen. When the fissure between the left upper lobe and lingula is not well developed, its position is indicated by a notch on the anterior margin of the lung. The fissure is commonly more pronounced on the mediastinal than on the costal surface of the lung (Fig. 2).

The lingula, when well developed, resembles the right middle lobe in shape and exhibits a quadrilateral mediastinal surface, a semielliptical inferior or interlobar surface, and a triangular anterolateral or costal surface. A prominent ridge or "frenum" separates the mediastinal and inferior surfaces and extends upward and backward to the hilum. In the posterior end of this ridge are situated the bronchus and blood vessels supplying the lingula.

Hovelacque *et al.*[6] have reported two cases of trilobar left lungs, and Chiari[2] another, in which the extrapulmonary course of the lingula bronchus

resembled that of the right middle lobe bronchus, having an independent origin from the left lower lobe stem bronchus.

The Lingula Bronchus.—The anatomy of the lingula bronchus was described by Ewart,[5] in 1889, in his monograph on the bronchi and pulmonary blood vessels. Ewart referred to the lingula as the "cardiac lobe," and on the evidence of dissections and bronchial casts described a "cardiac stem bronchus" arising from the inferior aspect of the upper lobe bronchus about 1 cm. from its origin, dividing after a 2 to 3 cm. course into anterior and posterior cardiac branches, the anterior again dividing into medial or sternocardiac, and lateral or mammary cardiac branches. Further subdivisions were described in detail.

The lingula bronchus arises from the inferior aspect of the left upper lobe

A B

FIG. 2.—Normal human left lung showing the lingula fissure well developed on the mediastinal surface, and the characteristic notch on the anterior border of the lung. The lingula bronchus has been dissected to demonstrate its origin from the upper lobe bronchus and its bifurcation.

bronchus 1 to 2 cm. from its origin and runs downward and forward. It terminates by division into two branches, an anterolateral and a posteromedial (Fig. 3).

In our own material, consisting of dissections of the human lung and lipiodol bronchograms, certain minor variations in the mode of origin of the lingula bronchus and the axillary branch of the upper lobe bronchus were encountered. Figure 4A represents the more common arrangement. Occasionally the lingula bronchus and the axillary branch of the upper lobe bronchus arise by a common stem from the main upper lobe bronchus as demonstrated in Figure 4B. Variations are also encountered in the distance of the orifice of the lingula bronchus from the orifice of the upper lobe

bronchus, and in the length of the lingula bronchus proximal to its first division.

The Blood Supply to the Lingula.—The branch of the pulmonary artery supplying the lingula arises from the main arterial trunk above the level of

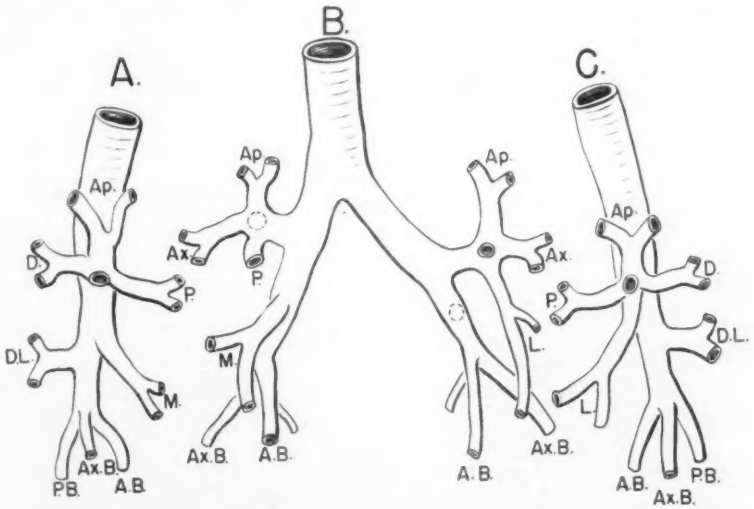

FIG. 3.—Diagrammatic representation of the normal bronchial tree. (A) Right lateral view. (B) Anteroposterior view. (C) Left lateral view. (Ap.) Apical division of the upper lobe. (Ax.) Axillary division of upper lobe. (P) Pectoral division of upper lobe. (D) Dorsal division of upper lobe. (L) Lingula bronchus. (M) Right middle lobe bronchus. (D.L.) Dorsal lobe bronchus. (A.B.) Anterior basic division of the lower lobe. (Ax.B.) Axillary basic division of the lower lobe. (P.B.) Posterior basic division of lower lobe.

the origin of the upper lobe bronchus, behind which it runs downward and laterally, continuing its course lateral and slightly posterior to the lingula bronchus (Fig. 5). The main artery divides into two branches which follow closely the two primary divisions of the lingula bronchus, the artery accom-

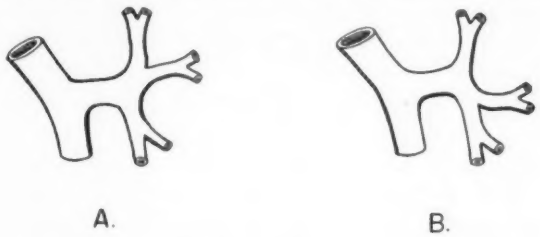

FIG. 4.—Diagrammatic representation of variations in the mode of origin of the lingula bronchus and the axillary division of the upper lobe bronchus. The arrangement shown in A is the more common.

panying the posteromedial division descending anterior to the anterolateral branch bronchus. The lingula veins run in a plane anterior to the bronchi and arteries, and drain into a main vessel running medial and slightly anterior to the lingula bronchus to join the inferior pulmonary vein. At the hilum of the lingula the vein, the bronchus and artery are encountered, in that order, dissecting laterally from the mediastinum.

Experimental Delineations of the Lingula Segment.—Injection experiments were undertaken to determine the projection areas on the surface of the lung of the bronchopulmonary segment supplied by the branches of the lingula bronchus. In the first series of normal human lungs, the main lingula bronchus, and in the second series, one of the two primary divisions were injected under pressure with a viscid solution of old roentgen films in acetone, colored with aniline-black dye. The advantage of this solution as an injection material lay in its tendency to harden into a solid mass, allowing the injected bronchopulmonary segment to be dissected from the remaining lung tissue, and its shape and relations to be determined. Figure 6 demonstrates the typical appearance of a normal lung following injection of the main lingula bronchus and inflation of the remainder of the lung, and shows the area of lung

A B

FIG. 6.—(A) Injection of the main lingula bronchus of a normal left lung to demonstrate the whole lingula segment. (B) Left upper lobe, mediastinal aspect.

surface in relation to that of the lingula segment. Injection of the posteromedial branch of the lingula bronchus filled the mediastinal segment of the lobe; when the anterolateral branch was injected the mass was confined to the costal segment. In a series of 20 injection experiments the bronchopulmonary segments supplied by the lingula bronchus were found to be constant in size, position and configuration.

Clinical Visualization of the Lingula Bronchus by Lipiodol Bronchography.—A modification of the bronchography technic, evolved by Erwin,[4] was employed in obtaining the bronchograms reproduced in this article. The patient receives sodium pentobarbital Gr. 1½ one-half hour before the injection. The preliminary use of this drug appears to diminish the incidence of cocaine reaction. The pharynx and one nostril are sprayed with 4 per cent cocaine solution containing adrenalin; cotton pledgets soaked in the same solution are held in each pyriform fossa on Negus laryngeal forceps for two minutes to anesthetize the superior laryngeal nerves. A fine, rubber urethral

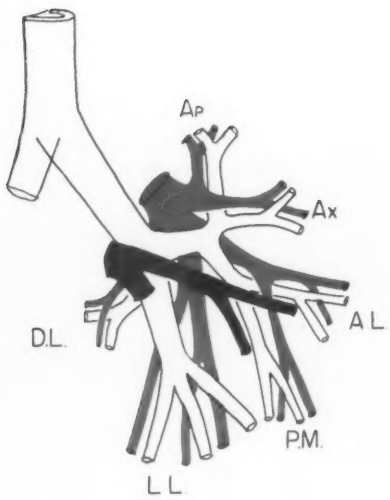

Fig. 5.—Diagrammatic representation of the blood supply to the lingula. Branches of the pulmonary artery shown in red and the veins in blue. (Ap.) Apical division of upper lobe. (Ax.) Axillary division of upper lobe. (A.L.) Anterolateral division of the lingula. (P.M.) Posteromedial division of the lingula. (D.L.) Dorsal lobe branches. (L.L.) Lower lobe branches.

catheter is passed through the cocainized nostril while the patient forcibly draws his tongue forward; the tip of the catheter shows a natural tendency to enter the larynx and passes easily between the cords. Having entered the trachea, 2 cc. of cocaine solution are injected through the catheter to anesthetize the tracheal and bronchial mucosa and suppress the cough reflex. The tip of the catheter lies in the lower third of the trachea and no attempt is made to pass it into the bronchi.

Certain general principles are observed during the injection. The lipiodol is used cold; when warmed the viscosity is diminished and the oil tends to run out into the alveoli. The oil is injected slowly and the cough reflex held completely in abeyance. Twenty cubic centimeters of oil are sufficient to outline both bronchial trees in an adult, less being required in a child. More information concerning bronchial pathology can be obtained by outlining the bronchial lumen with a thin, evenly distributed film of oil than by complete filling of the lumen. The side, or the suspected side, of the disease is filled first. Ideally, each lung should be filled and examined independently at three-week intervals in order that a true lateral as well as an anteroposterior film of each bronchogram may be obtained. It is not always practicable to do this and, when both lungs are to be examined at the same time, it is usual first to fill the suspected side and make the anteroposterior and lateral exposures; the other lung is then filled and further anteroposterior and oblique exposures are made. Lateral films taken with both lungs filled are dangerously misleading, owing to the superimposition and confusion of the two bronchial patterns.

With the catheter in position, the patient is placed horizontally upon the table with his shoulders supported on two pillows and the body half turned toward the left side; 6 cc. of oil are slowly injected into the dorsal lobe and dorsal branches of the lower lobe bronchus. The patient is then instructed to sit up, to bend forward, and lean toward the left side; 3 cc. of oil are then injected into the middle lobe or lingula bronchus and into the anterior branches of the lower lobe bronchus. The pillows are then removed and the patient lies down and is completely turned onto his left side; 3 cc. of oil are then injected into the upper lobe bronchus and lateral branches of the lower lobe bronchus. A left lateral exposure is then made with the patient lying on his left side; an anteroposterior picture with the patient lying flat on his back; and, if the left lung alone is being examined, a right oblique exposure is made in the standing position. If both lungs are being examined, the patient is turned toward the right side after lateral and anterioposterior exposures of the left side have been made, and the remaining lipiodol distributed between the three positions corresponding to those used for the left lung. Less lipiodol is required to fill the second side as some tends to run over from the bronchi previously filled. Anteroposterior and right oblique exposures are then made with the patient in the erect position. The position which best demonstrates the anatomic relations of the lingula bronchus is the right oblique with the patient in the erect position (Fig. 7). The advantage

of using a rubber intratracheal catheter, through which to inject the oil, lies in the ease with which the posture of the patient can be changed during the injection.

Interpretation of the Bronchogram.—No opinion can be based upon a single anteroposterior view; lateral and oblique views are essential for the interpretation of the bronchogram. The anatomy of the normal or diseased lingula can be determined only if its bronchus is completely outlined throughout its entire course, and its origin from the upper lobe bronchus clearly traceable, conditions which presuppose adequate filling of the upper lobe bronchus. Its first descending branch will be recognized as the lingula bronchus. Figures 8 to 11 demonstrate variations in the appearance of the bronchograms of the normal lingula bronchus in the three positions: anteroposterior, left lateral and right oblique. The lingula bronchus is apt to be confused with the lower lobe bronchi in the anteroposterior position, but their differentiation presents no difficulties in the left lateral and right oblique positions. Reference to the diagrams in Figures 3, 4 and 7 will assist in the interpretation of these bronchograms, and the identification of the various branch bronchi. The position of the lingula as visualized on the bronchogram varies with the condition of the lower lobe. In general it is situated more laterally when the lower lobe is normally aerated than when it is collapsed. After left lower lobe lobectomy the lingula swings downwards and posteriorly.

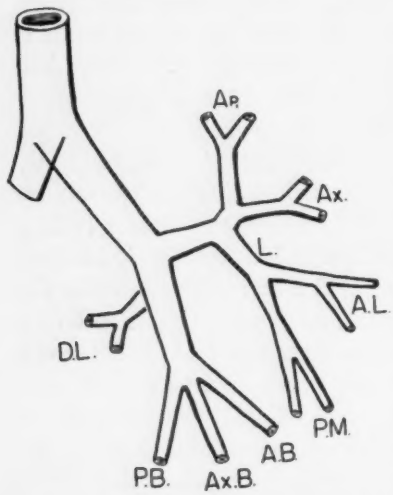

FIG. 7.—Diagrammatic representation of the normal left bronchogram, as visualized in the right oblique view. The distance between the orifice of the lingula bronchus and the orifice of the upper lobe bronchus has been slightly exaggerated. (Ap.) Apical division of upper lobe. (Ax.) Axillary division of upper lobe. (L.) Lingula. (A.L.) Anterolateral division of the lingula. (P.M.) Posteromedial division of the lingula. (D.L.) Dorsal lobe. (A.B.) Anterior basic division of lower lobe. (Ax.B.) Axillary basic division of lower lobe. (P.B.) Posterior basic division of lower lobe.

Bronchiectasis of the Lingula Process.—In the present series of 86 cases of bronchiectasis operated upon at the Massachusetts General Hospital (by E. D. C.), there were 55 cases in which the left lower lobe was removed as the major focus of the disease. In 44, or 80 per cent, of these 55 cases the lingula was also resected because of demonstrable bronchiectasis. In 108 cases of bronchiectasis of the left lower lobe operated upon at the Brompton Chest Hospital, London, the lingula was involved in 81, or 75 per cent.[1] These statistics demonstrate the great frequency with which resection of the lingula in addition to the removal of the left lower lobe is necessary to eradicate bronchiectasis of the left lung. Figures 12 and 13 demonstrate the bronchograms of two typical cases of bronchiectasis of the lingula and left lower lobe.

It has been observed that commonly the posteromedial branch of the lingula bronchus alone is diseased and only rarely are both branches involved.

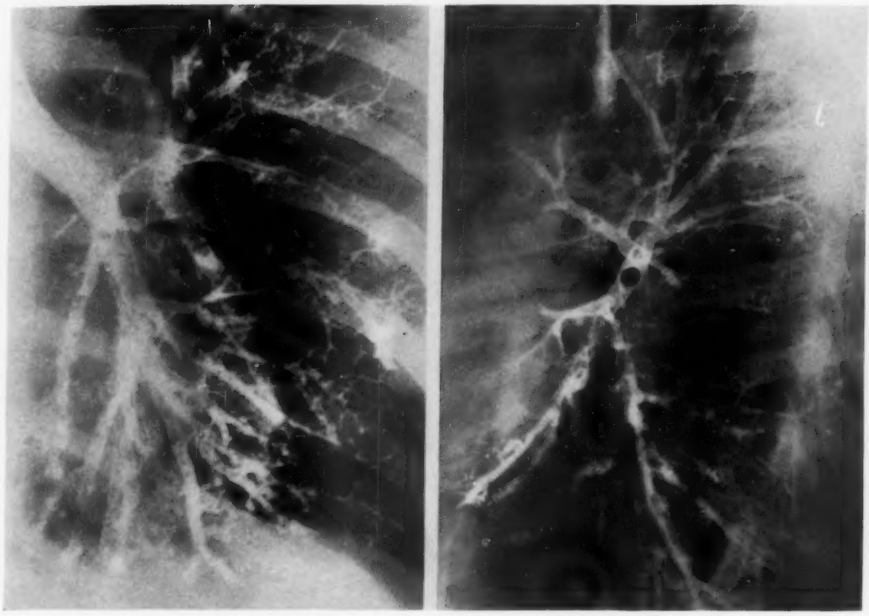

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FIG. 8.—Normal left bronchogram. (A) Anterolateral view. (B) Left lateral view. In the lateral view, the lumen of the axillary branch of the upper lobe bronchus is seen end-on as a dark circle.

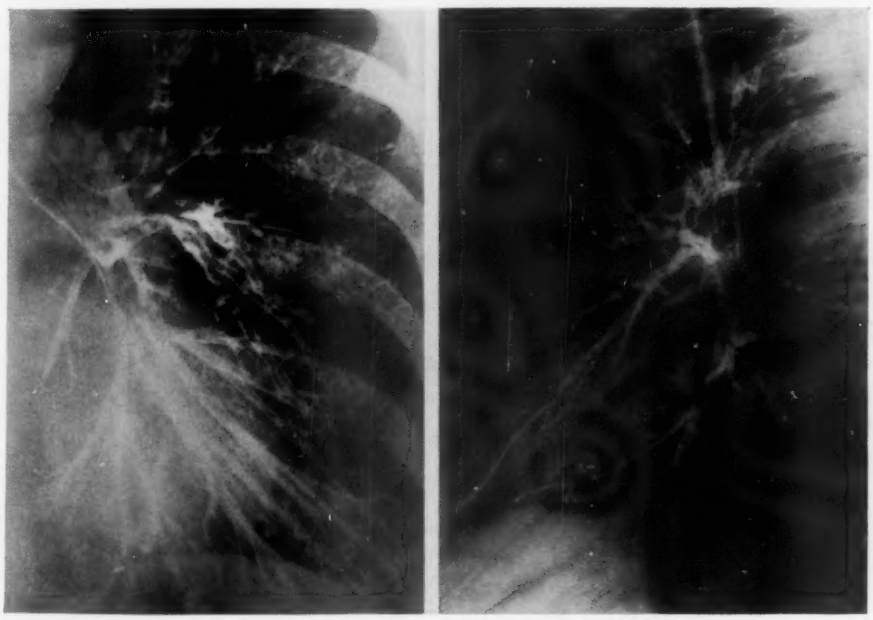

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FIG. 9.—Normal left bronchogram. (A) Anteroposterior view. The pectoral branch of the upper lobe bronchus is seen descending anterior to the anterolateral branch of the lingula bronchus, with which it should not be confused. (B) Left lateral view. Pectoral bronchus well shown just above lingula bronchus.

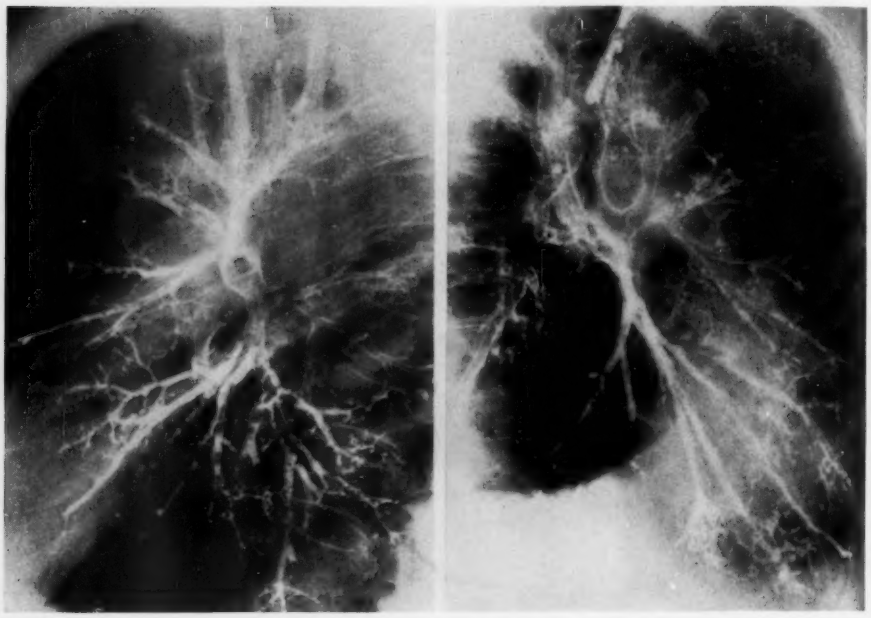

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FIG. 10.—Normal left bronchogram. (A) Left lateral view. (B) Right oblique view. Owing to the upward obliquity of the left upper lobe bronchus, the lingula bronchus appears to arise abnormally high in the left lateral view. Origin with axillary branch as shown in Figure 4B.

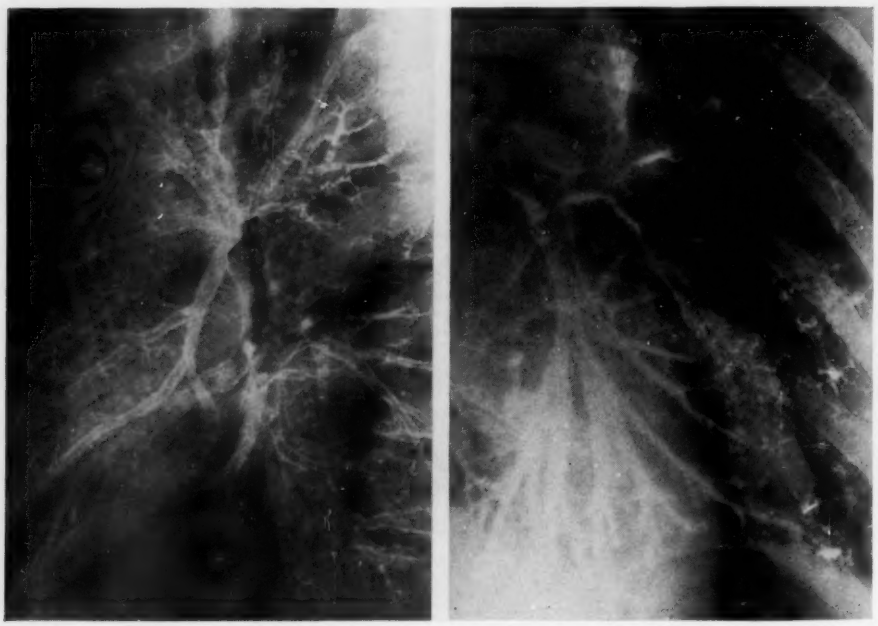

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FIG. 11.—Normal left bronchogram demonstrating the lingula bronchus and its primary divisions. (A) Left lateral view. (B) Right oblique view (see Fig. 7).

Bronchiectasis may be confined to, or predominant in the lingula process, but this distribution is not common, and was encountered only four times in a series of 50 cases of bronchiectasis studied by complete bronchograms. Figure 14 demonstrates a case of bronchiectasis confined to the lingula process and of sufficient severity to cause disabling symptoms. Figure 15 demonstrates a case of bronchiectasis predominant in the lingula process but with minimal involvement of a single bronchus in the left lower lobe. In Figure 16 is shown bronchiectasis of the anterolateral segment of the lingula and the right middle lobe, an unusual combination.

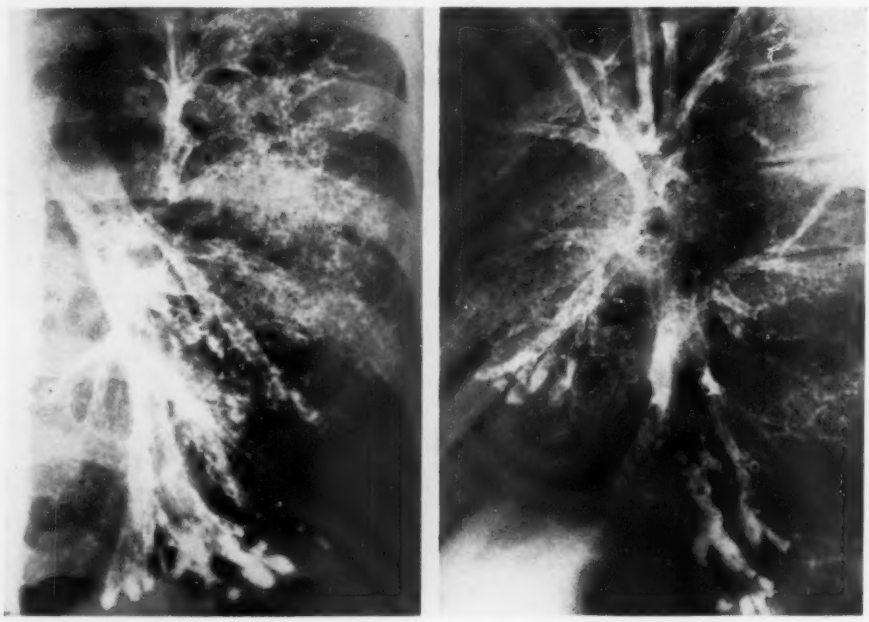

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FIG. 12.—Cylindric bronchiectasis of the left lower lobe and posteromedial divisions of the lingula bronchus. (A) Anteroposterior view. (B) Left lateral view.

Residual Lingula Bronchiectasis.—Despite the fact that the lingula has been resected with the left lower lobe in 80 per cent of the Massachusetts General Hospital series, at least two patients have been observed with residual symptoms due to failure to recognize disease in this area or resect it at the time of operation. Before the perfection of bronchographic technic, the gross appearance of the lingula at the time of operation was taken as indication for or against resection. These unsatisfactory results demonstrate that this procedure, while usually adequate, is not wholly reliable.

Patients have also been seen following lobectomy in other clinics, who complain that after removal of the left lower lobe a considerable quantity of sputum has remained. Bronchography has revealed the presence of residual bronchiectasis in the lingula process. Review of the original bronchograms, on the basis of which the lobectomy was performed, revealed either an inadequate filling of the lingula bronchus, which rendered it impossible to

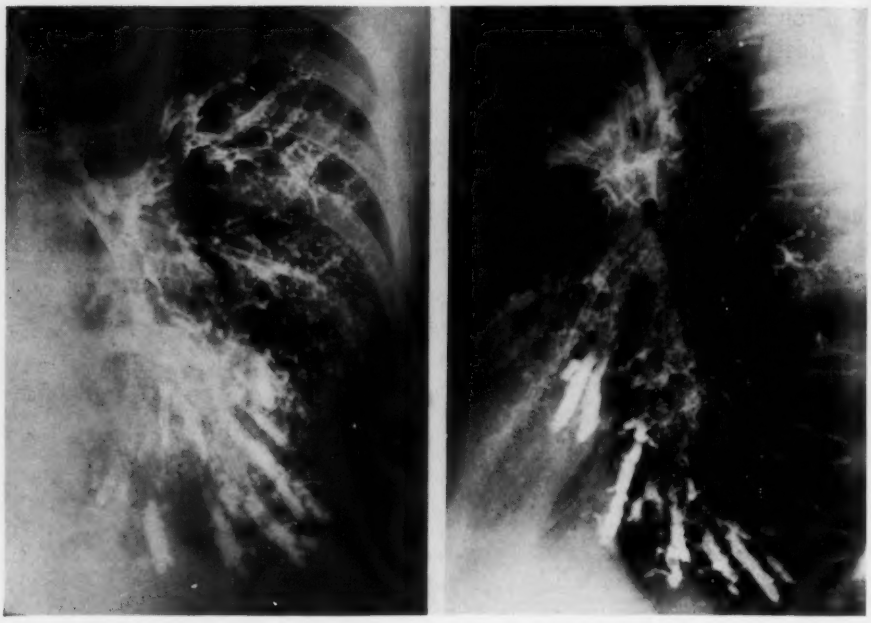

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FIG. 13.—Cylindric bronchiectasis of the left lower lobe and posteromedial divisions of the lingula. (A) Anteroposterior view. (B) Left lateral view. In the anteroposterior view, the diseased posteromedial branch of the lingula overlies dilated branches of the lower lobe bronchus, but is clearly differentiated from them in the lateral view. The anterolateral branch of the lingula is normal.

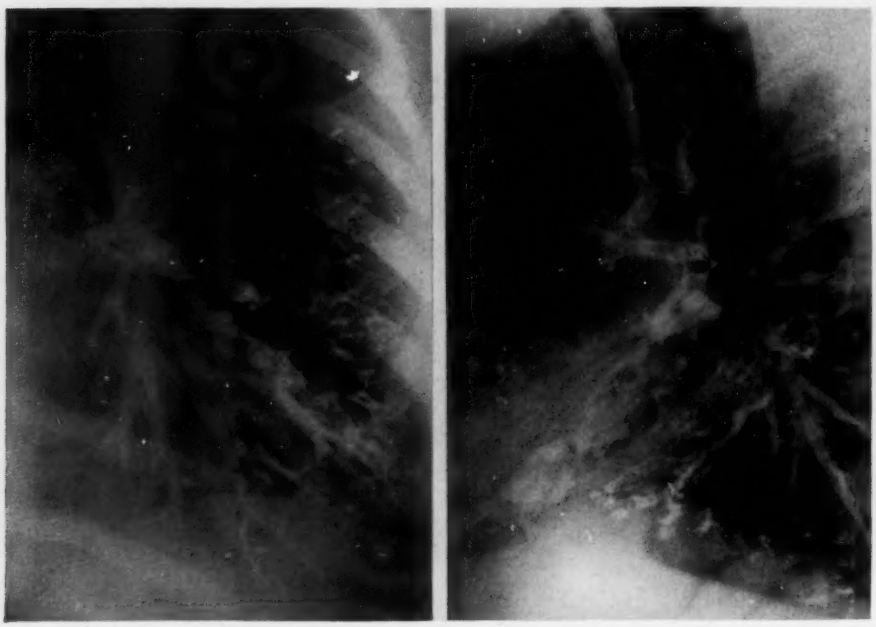

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FIG. 14.—Cylindric bronchiectasis of both divisions of the lingula bronchus. The left lower lobe is normal. (A) Anterolateral view. (B) Left lateral view.

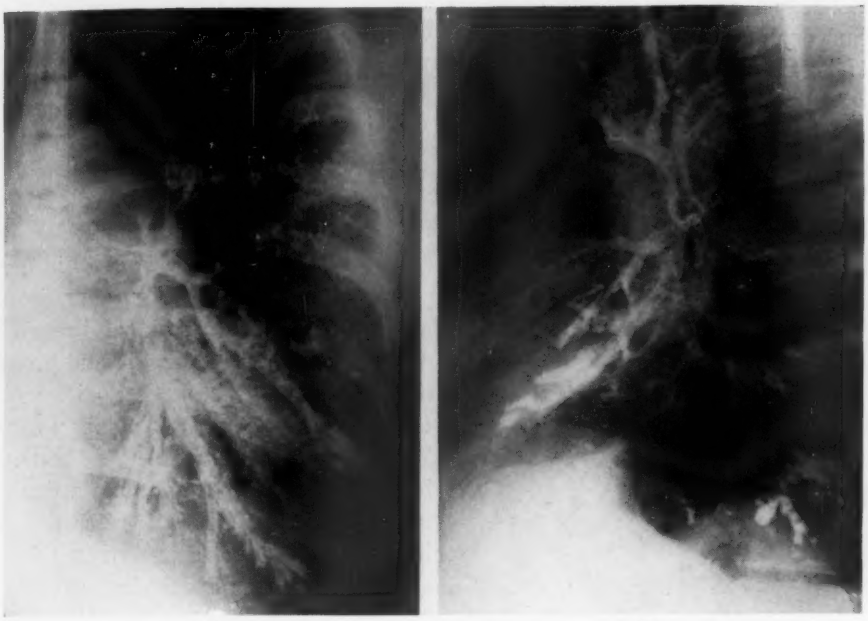

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FIG. 15.—Cylindric bronchiectasis of both divisions of the lingula bronchus, associated with minimal disease in a single lobule of the lower lobe. (A) Anteroposterior view. (B) Left lateral view. In the lateral view, note that the pectoral branch of the upper lobe bronchus has been drawn downward toward the lingula bronchus, and that one of its terminal branches is dilated.

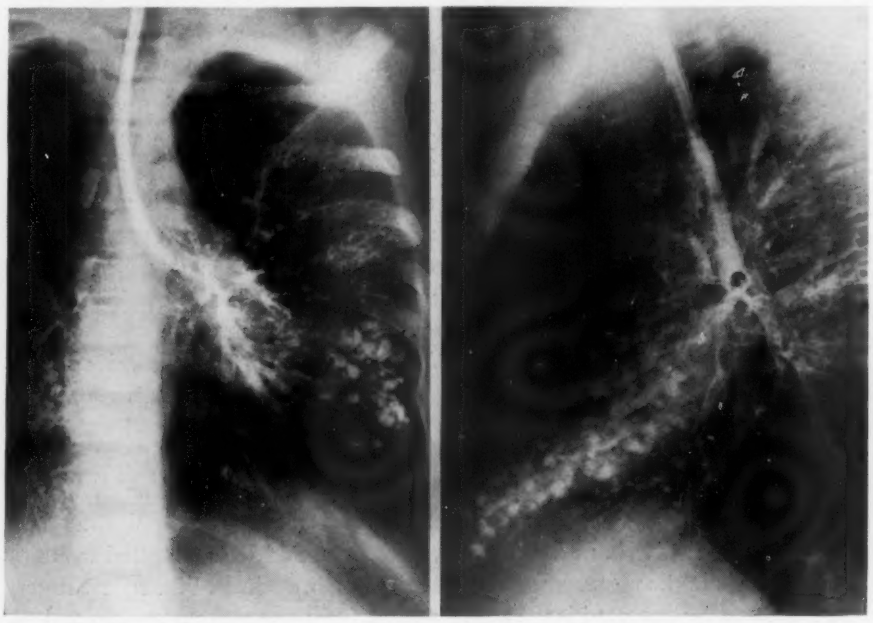

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FIG. 16.—Saccular bronchiectasis of the lingula; disease is also present in the right middle lobe. (A) Anteroposterior view. (B) Left lateral view. In the anteroposterior view, the saccular dilatations appear to communicate with the branches of the axillary basic division of the left lower lobe bronchus, but the left lateral view localizes the bronchiectasis to the lingula, and demonstrates the lower lobe to be normal.

visualize the disease present therein, or failure to interpret the film correctly. Surgery of this type will quickly cast disrepute upon the surgical treatment of bronchiectasis just as it is beginning to live down a somewhat unsavory reputation.

Persistence of symptoms due to lingula bronchiectasis is to be differentiated from the production of secretion by granulation tissue in an abnormally large lower lobe "stump," or a small persistent empyema pocket draining through the stump of the lower lobe bronchus. Both of these conditions are known to be associated with persistent cough and sputum, at least early in the postoperative period. Figure 17 demonstrates a case of residual bronchiectasis present in the lingula and probably causing the persistence of symptoms following a lower lobe lobectomy. The qualification is made deliberately because sufficient data are not at hand to evaluate properly the rôle of the lobar stump as a cause of residual sputum. In this particular case the stump is short and presumptive evidence incriminates the lingula.

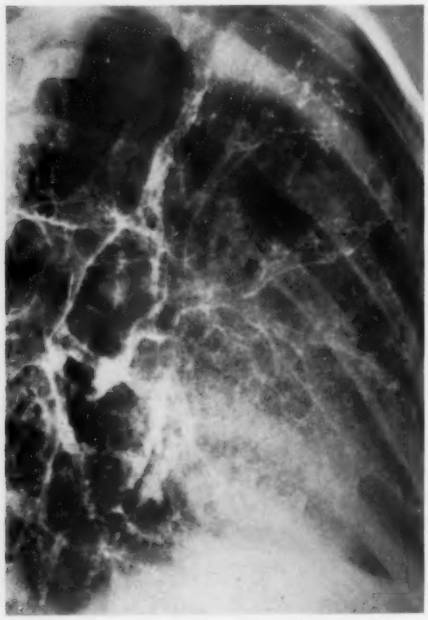


FIG. 17.—Postlobectomy bronchogram demonstrating the stump of the lower lobe bronchus, and residual bronchiectasis in the lingula, which has been displaced downward and backward. Right oblique view.

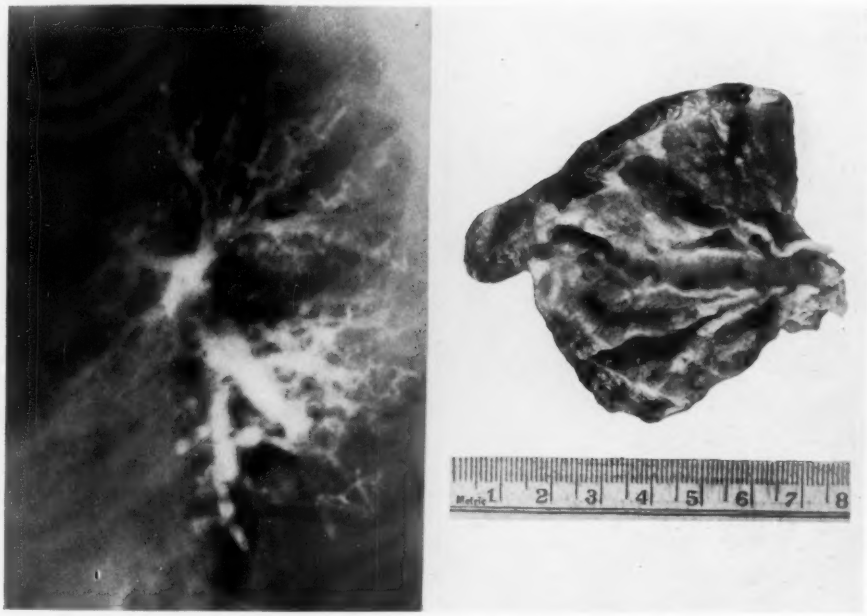
Figure 18 shows the postlobectomy bronchogram of a patient who complained that the removal of the lower lobe had only slightly diminished the volume of sputum. Bronchography revealed the presence of a residual lingula bronchiectasis. The stump of the lower lobe was also well filled by lipiodol but the operative note indicated a higher amputation than usual. Bronchoscopy disclosed a dry stump completely epithelialized and an inflamed lingula bronchus full of pus. The lingula was resected in this case with complete relief of symptoms.

Chronic Pulmonary Abscess of the Lingula.—In the clinical material forming the basis of this paper, there has occurred one case of abscess confined to the lingula, in a male, age 19. The abscess had been drained externally in the acute stage seven years previously; the wall of the cavity had become epithelialized and an external bronchial fistula persisted. Injection of lipiodol through the bronchocutaneous fistula outlined a cavity communicating with the anterolateral division of the lingula bronchus, and demonstrated cylindric bronchiectasis in the posteromedial division of the bronchus (Fig. 19). Surgery was indicated by repeated large hemorrhages from the abscess cavity, and the lingula process was excised through an anterolateral approach.

OPERATIVE TECHNIC.—The lingula is usually resected at the time the lower

lobe is removed and is readily accessible through the usual posterior incision. In the few instances in which the lingula alone has been resected, an anterolateral approach, similar to that employed for a middle lobe lobectomy, has been found satisfactory.

It has been considered advisable to complete the lower lobe lobectomy, including closure of the hilar stump, before dealing with the lingula. Then the tip of the lingula is grasped with lung forceps and as adhesions that may be present are severed, it is drawn sharply upward and laterally, throwing the "frenum" into prominence. Adhesions to the pericardium in the line of the pericardiophrenic vessels may be troublesome, and at times the phrenic



A B

FIG. 18.—Postlobectomy bronchogram revealing residual bronchiectasis in the lingula, two years after left lower lobectomy for bronchiectasis. (A) Left lateral view. Note how the lingula has been displaced downward and backward. Some of the shadow cast by the lipiodol is undoubtedly cast by the stump which was carefully surveyed at the secondary operation and found to be a contracted nodule of scar tissue at the hilum. (B) Resected lingula.

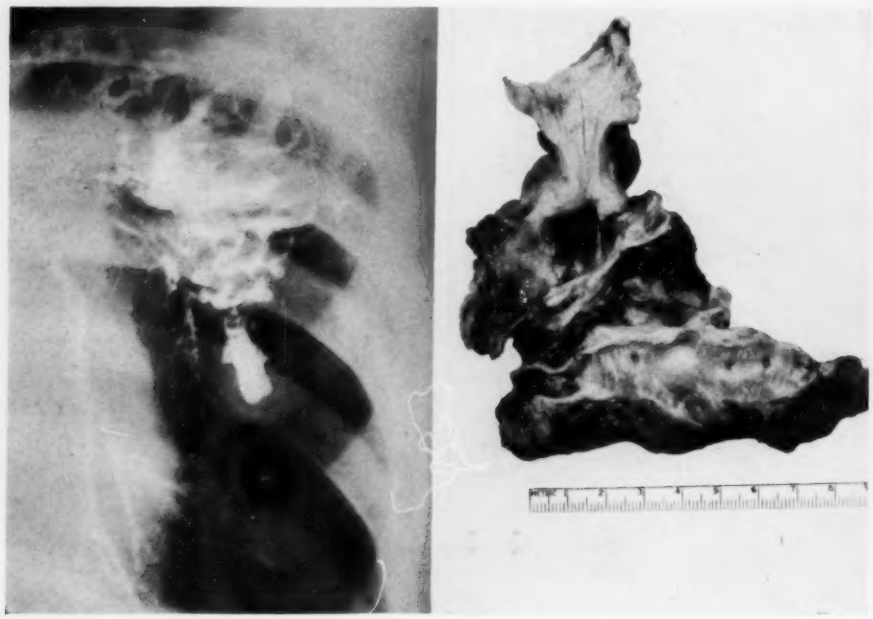
nerve is jeopardized as it tends to separate from the pericardium by traction on the adhesions.

Dissection into the hilar region is started at the base of the frenum, separating the lung parenchyma from the mediastinal pleura until the bronchus and its related blood vessels are exposed (Fig. 20). The vessels are divided between ligatures, taking pains to avoid injuring the artery to the lower lobe in case the lower lobe has not been removed.

The anesthetist is then instructed to release the positive intratracheal pressure, allowing the upper lobe to deflate. A light clamp is applied to the bronchus with sufficient pressure to occlude its lumen but not crush the walls. The lobe is now reinflated by restoring the positive intratracheal pres-

sure. The lingula bronchopulmonary segment remains atelectatic (Fig. 21). This maneuver not only positively identifies the bronchus but delineates the relatively avascular cleavage plane for section of the lung parenchyma.

Division of the lung is now made with the aid of curved clamps placed in the form of a T, the vertical line parallelling the course of the "frenum" and stopping at the bronchus which is now amputated. The plane between inflated and deflated alveoli is always discernible and the clamps are placed just on the atelectatic side to allow greater freedom in suturing. Running stitch ligatures are then placed on the lung substance held by the clamps. The bronchus is closed by a circular ligature, or simple plastic procedure, and adjacent lung tissue is drawn over the stump. Finally, a running suture



A B

FIG. 19.—Chronic lung abscess of the anterolateral segment of the lingula, and secondary bronchiectasis in the posteromedial segment. (A) Anterolateral view after injection of lipiodol through the chronic chest wall sinus. (B) The lingula after removal, showing the abscess cavity, and the cylindric bronchiectasis in the adjacent bronchi.

on an atraumatic needle buries the hemostatic sutures and brings visceral pleurae together in a neat T-shaped line. Lobules closely adjacent to the suture line may become filled with blood, but on the whole the procedure is attended by very little hemorrhage if the segmental vessels have been properly secured and the avascular cleavage plane followed. If the ligature has been placed only on the posteromedial division of the artery, as may be done by mistake, brisk hemorrhage will be encountered from the anterolateral division as the hilum is approached.

The anesthetist should now vary the intratracheal pressure allowing the

remaining portion of the upper lobe to deflate and inflate, thus demonstrating the integrity of the remaining bronchial divisions.

If preoperative bronchograms have clearly demonstrated a normal anterolateral division of the lingula bronchus, only the posteromedial segment need be resected. To this purpose the lung parenchyma is divided between clamps at the base of the "frenum" without exposing the structures at the hilum. The bronchus may be identified by palpation and a stitch ligature thrown about it. Adjacent vessels are clamped and ligated and bleeding from the lung parenchyma controlled with curved clamps as described above. As this dissection does not follow an avascular cleavage plane, it is attended by more

FIG. 20.—Dissection of the hilum of the lingula, as approached anteriorly with the tip of the lingula elevated. The bronchus lies in the center with the vein at its medial aspect and the artery situated laterally.

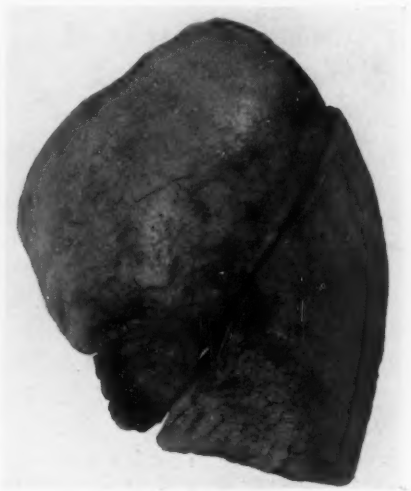


FIG. 21.—Appearance of normal lung, inflated after obstruction of the lingula bronchus. The line of demarcation between the atelectatic lingula and the aerated upper lobe is clearly discernible.

bleeding, but if the dissection is carried from the hilum outward, it may be reduced to a minimum. Figure 22 demonstrates a posteromedial segment of the lingula bronchus removed by this method. Figure 23 is worthy of note in this connection. It has already been stated that involvement of the posteromedial division alone appears to be the commonest lesion of the lingula.

Discussion.—Anyone with much experience in the surgery of bronchiectasis will realize that in many cases dense adhesions and active infection producing the so-called "frozen hilum" will make the dissection of hilum structures exceedingly hazardous or impossible. Interlobar fissures may be so fused that they cannot be identified. However, as less severe cases of the disease present themselves for surgical treatment, refinements of technic may be directed toward the conservation of normal lung tissue. This is particularly important if involvement of the contralateral lung indicates a program of bilateral operations.

The dorsal segment of the lower lobe is found free of disease in a con-

siderable number of cases of lower lobe bronchiectasis. Employing the principles described above for resection of the lingula, the lower lobe has been divided in two cases, preserving the large dorsal segment with its bronchus and vascular supply intact. In both of these patients the lingula was resected at the same time. The same deflation technic was employed to delineate the avascular plane for section of the lower lobe.

FIG. 22.—Posteromedial segment of the lingula process following excision for bronchiectasis.

Postoperative Complications.—It has already been stated that the lingula has been resected with the left lower lobe in 44 cases. It has also been resected without removal of the lower lobe in one instance, and at a period subsequent to lower lobe lobectomy in one instance. There have been no deaths in this series. Bronchial fistulae have closed spontaneously with the exception noted below.

In one instance (Hosp. No. 18196) a patient was found sputum-free with healed fistula and incision two months after the operation (removal of left lower lobe and lingula). At the end of the third month, following a severe upper respiratory infection, an abscess developed in the left upper lobe, requiring drainage and establishing large bronchial fistulae that will require plastic closure. This complication may or may not be attributable to the lingula resection, or may be due to the fact that only the posteromedial division was removed, leaving residual bronchiectasis in the anterolateral segment.

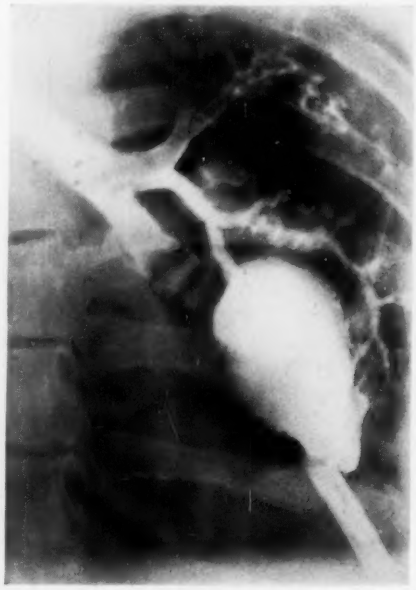


FIG. 23.—Lipiodol injection through the chest wall sinus, after removal of the left lower lobe and the posteromedial segment of the lingula, demonstrating a residual empyema pocket communicating through a bronchial fistula with the posteromedial division of the lingula bronchus. The anterolateral division of the bronchus is normal.

One very definite complication appears to attend the removal of a single bronchial segment that is not as frequent when an entire lobe is removed by the tourniquet technic. It has appeared in a high percentage of middle lobe lobectomies. The amputation of a large bronchus close to the main stem of the bronchial tree appears to favor obstructive atelectasis in closely adjacent areas of lung. After a middle

lobe lobectomy, complete or partial atelectasis of the lower lobe may persist for a period of three to four weeks. It is attended by cough and mucoid sputum that subsides as the lobe reexpands. The same happening has been observed in the upper lobe following complete resection of the lingula but does not often appear if the posteromedial division alone is resected. It has also occurred in the dorsal segment of the lower lobe after resection of the inferior segment.

This is not a surprising event and is readily explained by the inflammatory edema that must surround the focus of secondary healing in the bronchial tree. To minimize this complication, trauma is to be avoided in closing the bronchus and fine absorbable suture material employed. In a one stage operation in a free pleural cavity particular attention is to be paid to postoperative expansion of the lung.

Just how important this complication will be as a hazard of segmental resection of the lung remains to be seen. The advantage of a smaller residual empyema pocket when healthy lung is conserved is to be balanced against it.

SUMMARY

The anatomy of the lingula segment of the left upper lobe is considered. The lingula bronchus and blood vessels are described.

The bronchogram of this particular segment is illustrated.

Indications for surgical removal of the lingula are discussed and operative technics described.

More general applications of the principle of segmental pneumonectomy are indicated, particularly with reference to the lower lobes.

It is suggested that the bronchopulmonary segment may replace the lobe as the surgical unit of the lung.

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THE GRADING AND PROGNOSIS OF CARCINOMA OF THE COLON AND RECTUM

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SINCE 1893, when Von Hansemann[1] first attempted to grade the malignancy of tumors by their histology, many pathologists have made similar studies on all varieties of tumors. Most have agreed that grading is of some value in prognosis, but have disagreed as to how much. Others have not found it of any significance. Studies on colon and rectal tumors have been made chiefly by Rankin and Broders,[2] Rankin,[3] Rankin and Olson,[4] Dukes,[5, 6] Stewart and Spies,[7] Wood and Wilkie,[8] and Raiford.[9] Each was convinced of the importance of grading in prognosis, but did not always use the same method. Rankin and Broders divided the tumors into four grades according to the relative proportion of differentiated and undifferentiated cells. Dukes used this method also. Stewart and Spies based their grades on the number of mitoses, the amount of papillary formation, the degree to which the polarity of the cells and their nuclei had been maintained, and the preservation of adenoid structure. Wood and Wilkie adopted a similar method, based mainly on low power magnification, but apparently did not use the frequency of mitosis as a criterion. MacCarty[10] advocated other criteria, based on changes in the stroma, such as lymphocytic infiltration, fibrosis, and hyalinization. Other pathologists have used still other methods for estimating the malignancy of tumors. In a recent study of a series of carcinomata of the breast, Haagensen[11] has, for the first time, attempted to determine statistically the value of the various criteria used. Fifteen in all were studied, involving differences in the growth of cells, differences in cell morphology, and differences in the reaction of the stroma. Six were found to have prognostic significance and were used to determine the grades of the tumors in his series. These criteria were the papillary structure, comedo character, adenoid arrangement, variations in size and shape of the nuclei, the number of mitoses, and gelatinous degeneration. Of course, criteria which are of value in breast cancer are not necessarily suitable to apply to other types. In each type of tumor, they should be redetermined by such a study as Haagensen has made. In the present series, this has been attempted.

This series includes all the cases of carcinoma of the colon and rectum admitted to the Presbyterian Hospital from 1916 to 1932, inclusive, upon whom a resection had been performed with the expectancy of possible cure of the patient and in which cases microscopic sections were available. Both

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the colon and rectal tumors were studied together, as their pathology is essentially the same. Cases treated by palliative operations were not included. In the right colon, the operations were all ileocolic resections. In the left colon, which included the sigmoid, various types of resections, many of the Mikulicz type, were used. In the rectum and rectosigmoid, the operations included resections, perineal proctectomies and abdominoperineal operations in one or more stages.

The 225 tumors in the series were about equally divided between the colon and rectum. Of the 114 colon carcinomata, 20 per cent were found in the cecum, ascending colon, and hepatic flexure; 23 per cent in the transverse colon; 15 per cent in the splenic flexure and descending colon; and 42 per cent in the sigmoid. The low total for the cecum, ascending colon, and hepatic flexure and the high figure for the sigmoid are somewhat unusual. In eight of the 19 cecum and ascending colon cases, in which the origin of the tumor could be determined, it began at the medial and posterior wall of the gut. Craig and MacCarty[12] have emphasized the frequency of this site of origin. All eight of the cecal growths and one of the ascending colon showed involvement of the ileocecal valve. Craig and MacCarty found it involved in 64 per cent of 100 cancers of the cecum.

There were 223 cases operated upon. Of these, 18 were lost to follow-up, 59 were classed as operative deaths, nine died from other causes without evidence of recurrent disease, and 11 were without adequate microscopic sections. The remaining 126 cases were alive five years after operation, with or without disease, or died within five years from the disease.

In judging the criteria for grading, only five-year survivals, with or without disease, and those dead from the disease within five years, were considered. The operative deaths, those lost to follow-up, and those dead from other causes were not included. A better basis of comparison is possible when these cases have been excluded. In estimating the results of surgical treatment, however, or when one type of therapy is to be compared with another, these cases should be included. This point has been especially emphasized by the Cancer Commission of the League of Nations.[13] The results were expressed by both the percentage of five-year survivors after operation and of those alive over five years without evidence of disease. As there were only seven cases surviving over five years that had recurrences out of 68 five-year survivors, or about 10 per cent, the two sets of figures run fairly parallel. Two of these patients lived for eight years after operation before succumbing to the disease. Many patients were followed much longer than five years. The longest follow-up was 20 years. Follow-up results were based on actual examination of the patient in nearly every case. In the whole series of cases, the five-year follow-up was 92 per cent complete. In the cases considered for judging the criteria and the grades of malignancy, it was 100 per cent.

THE CRITERIA FOR GRADING.—Guided largely by the experience of Haagensen in grading breast tumors, eight criteria were selected as most promising for study. They can be grouped as he has suggested according to the manner

of growth of the cells, the cell morphology, and the reaction of the stroma. None of those chosen for study belonged to the last group. Those based on the manner of growth of the cells were the papillary character, glandular arrangement, invasiveness, nuclear polarity, and extracellular "mucin" secretion. Those based on differences in cell morphology were the size of nuclei, the variation in size of nuclei, and the number of mitoses.

There is, perhaps, a slight amount of overlapping between some of these criteria. Invasiveness and loss in glandular arrangement, for example, may represent a somewhat similar histologic picture, yet they are not necessarily the same.

Microscopic sections were nearly always available from several regions

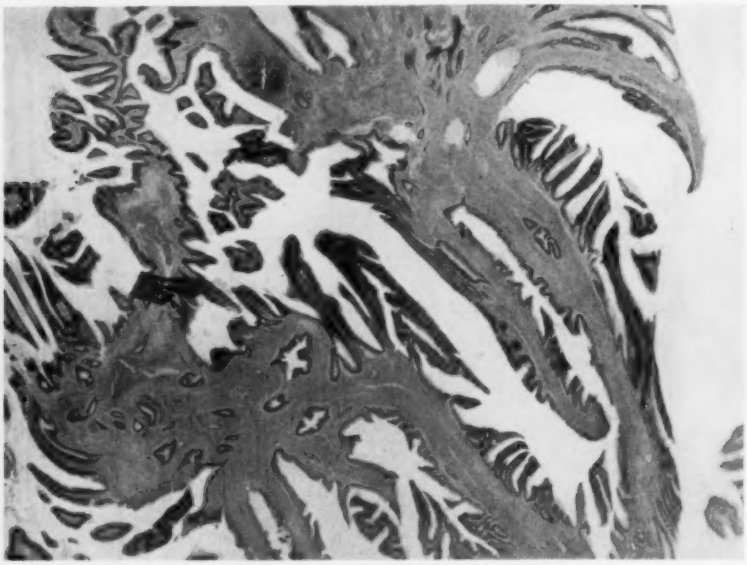

FIG. 1.—Carcinoma of the colon with marked papillary structure. (×33)

of the tumor. In most cases, these were stained with hematoxylin and eosin. In the more recent cases, Masson's anilin blue trichrome stain was also made. The mucicarmine stain for the presence of mucin, or more strictly speaking, mucicarminophilic substance, was used in about 52 per cent of cases.

Papillary Character.—Papillary structure is one of the outstanding features of the benign adenomata, and its presence in a malignant growth is usually taken as evidence of greater differentiation. Stewart and Spies have emphasized this point. Table I, however, shows only a slightly better follow-up result in cases in which papillary character was present. The chief disadvantage of this criterion is that it is usually present only in the superficial portions of the tumor and is replaced by the more typical glandular structure in the deeper layers. Sections taken through the surface of a tumor which has undergone considerable ulceration may fail completely to show this characteristic. It was, therefore, felt to be unreliable for prognosis.

TABLE I

PAPILLARY CHARACTERS

		Present	*Absent*
Cases	126	67	59
Five-year survivors:			
Cases	68	42	26
Per cent	54%	63%	44%
Five-year survivors without evidence of disease:			
Cases	61	38	23
Per cent	48%	57%	39%

Glandular Arrangement.—The tendency to form fairly regular tubules is a well recognized feature of an adenocarcinoma of low grade malignancy. The fact that in most cases in this series this characteristic was well marked

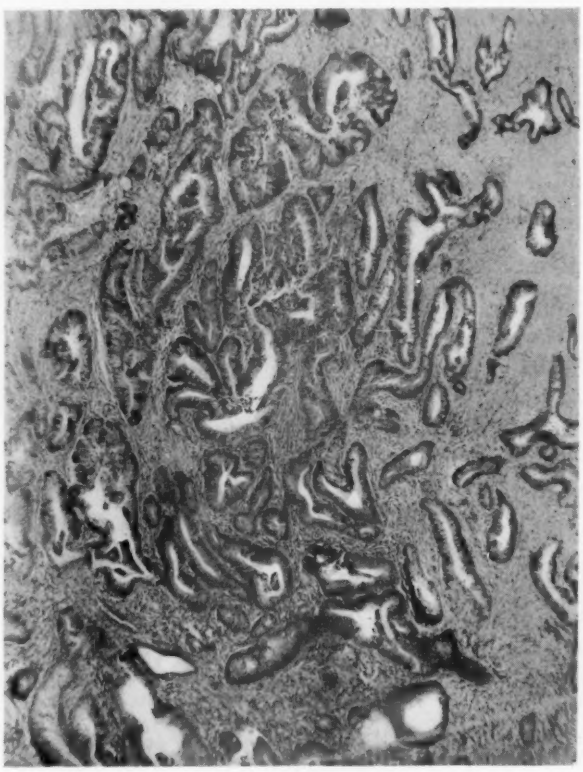

FIG. 2.—Carcinoma of the colon with marked adenoid arrangement of the cells. (×85)

supports the accepted view that carcinomata of the colon and rectum are in general relatively well differentiated. On the other hand, its absence in only a few cases limited its usefulness as a yardstick for grading. It proved, however, to be of value.

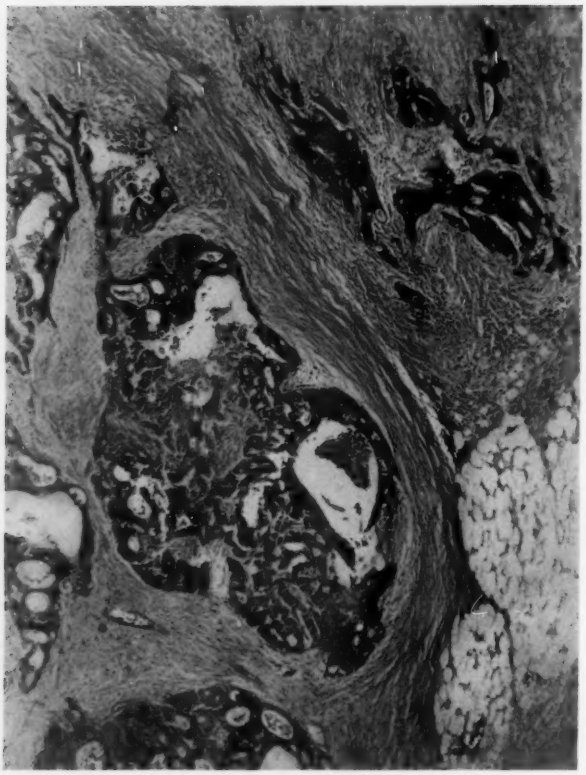

FIG. 3.—Carcinoma of the rectum with moderate adenoid arrangement of the cells. (×85)

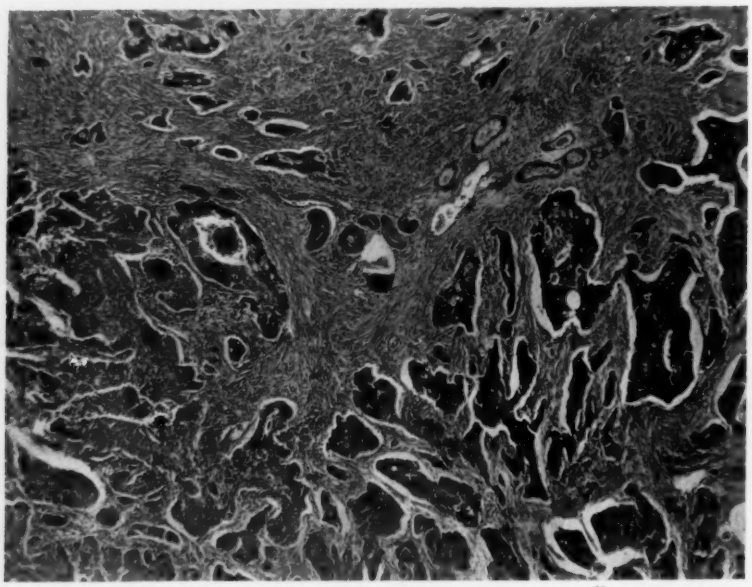

FIG. 4.—Carcinoma of the colon with slight adenoid arrangement of the cells. (×85)

TABLE II

GLANDULAR ARRANGEMENT

		Marked	*Moderate*	*Slight or Absent*
Cases	126	91	24	11
Five-year survivors:				
Cases	68	56	9	3
Per cent	54%	62%	38%	27%
Five-year survivors without evidence of disease:				
Cases	61	50	8	3
Per cent	48%	55%	33%	27%

Invasiveness.—This term was used to describe the tendency of tumor cells to appear to stream out singly or in small groups into the surrounding tissues. The basic adenoid structure may or may not have been lost. From the results, this criterion had greater prognostic value than any other.

Loss of Nuclear Polarity.—The term "nuclear polarity" is used here to describe the basal position of the nuclei in relation to the basement membrane of the gland tubule, rather than to their position in the cells. In the more differentiated tumors, the polarity of the nuclei is well preserved. Both the nuclei and the cells are arranged in several layers with the nuclei toward the basement membrane, and an outer clear zone of cytoplasm near the lumen. In the less differentiated tumors, the number of nuclear layers increases. The nuclei no longer maintain their basal position but may lie anywhere in the

TABLE III

INVASIVENESS

		Slight	*Moderate*	*Marked*
Cases	126	45	33	48
Five-year survivors:				
Cases	68	36	19	13
Per cent	54%	80%	56%	27%
Five-year survivors without evidence of disease:				
Cases	61	32	18	11
Per cent	48%	71%	55%	23%

gland wall, invading the cystoplasmic zone toward the lumen. Whether this change is due to the increase in the number of cell layers, to the loss of polarity of the nucleus within the cell, or to both, is not always apparent. The results showed this test to be of some significance.

"Mucin" Secretion.—The presence of varying amounts of "mucin" is of common occurrence in large bowel tumors. Broders,[14] Ochsenhirt[15] Rankin and Chumley,[16] and Parham[17] maintain that it is a product of secretion. They believe that the ability to secrete can be taken as a test of cellular differentiation, and that usually the greater the secretion the less the malignancy of the

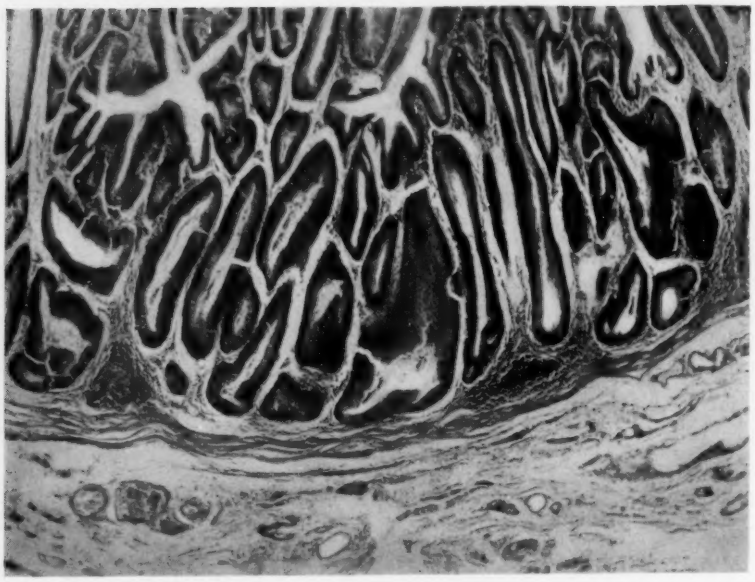

FIG. 5.—Carcinoma of the rectum showing very slight invasiveness. The tumor cells have not penetrated the muscularis mucosae. (×85)

tumor. Miles[18] and Boyd[19] consider it to be a degenerative change. Raiford[20] believes that the mucoid substance is due to oversecretion in the signet-ring

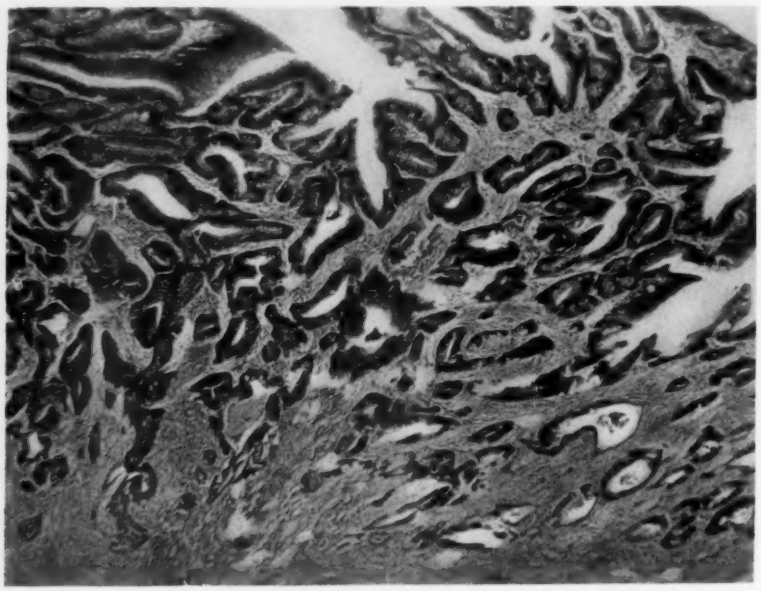

FIG. 6.—Carcinoma of the colon showing moderate invasiveness. (×85)

cell type of tumor, and to degeneration in the other "mucoid" tumors. In this study, the amount of the substance was judged by the amount in the lumen of the acini and in the tissues outside. Large lakes of "mucin" were frequently

seen scattered through the stroma. One criticism of this criterion is that much of this excess "mucin" may be the result of mechanical difficulties in drainage through the acini rather than to overproduction. Estimation of the amount of

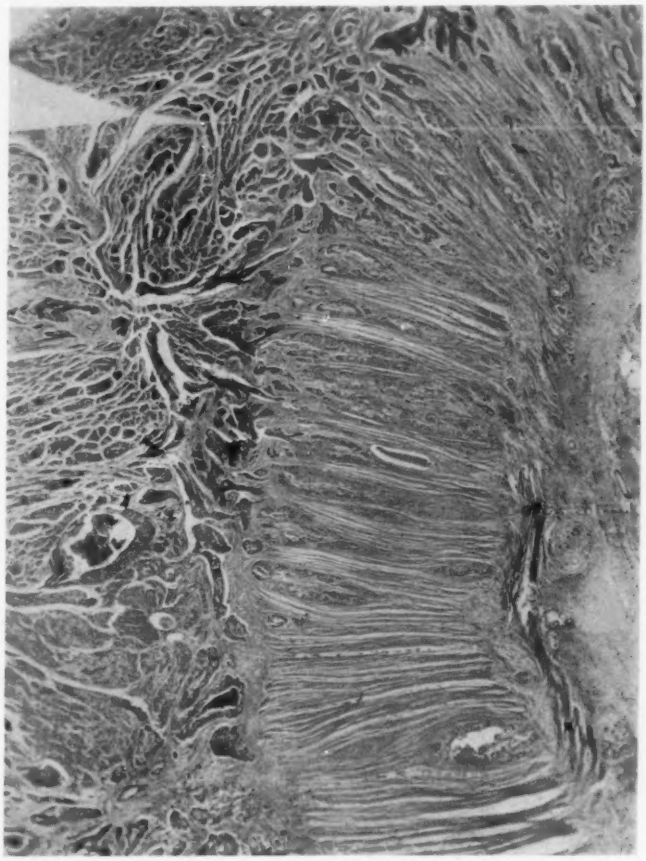

FIG. 7.—Carcinoma of the colon showing marked invasiveness. (×33)

intracellular "mucin" is difficult and was not attempted. However, when it appeared in the cells to the extent of crowding the nucleus to one side to

TABLE IV

LOSS OF NUCLEAR POLARITY

		Slight	*Moderate*	*Marked*
Cases	126	45	59	22
Five-year survivors:				
Cases	68	33	28	7
Per cent	54%	72%	47%	28%
Five-year survivors without evidence of disease:				
Cases	61	28	27	6
Per cent	48%	62%	46%	27%

give the characteristic appearance of the signet-ring type of tumor, it was carefully noted.

There were 15 cases classed as "mucoid" or "colloid" tumors with follow-ups suitable for grading. In these cases, the "colloid" substance occupied

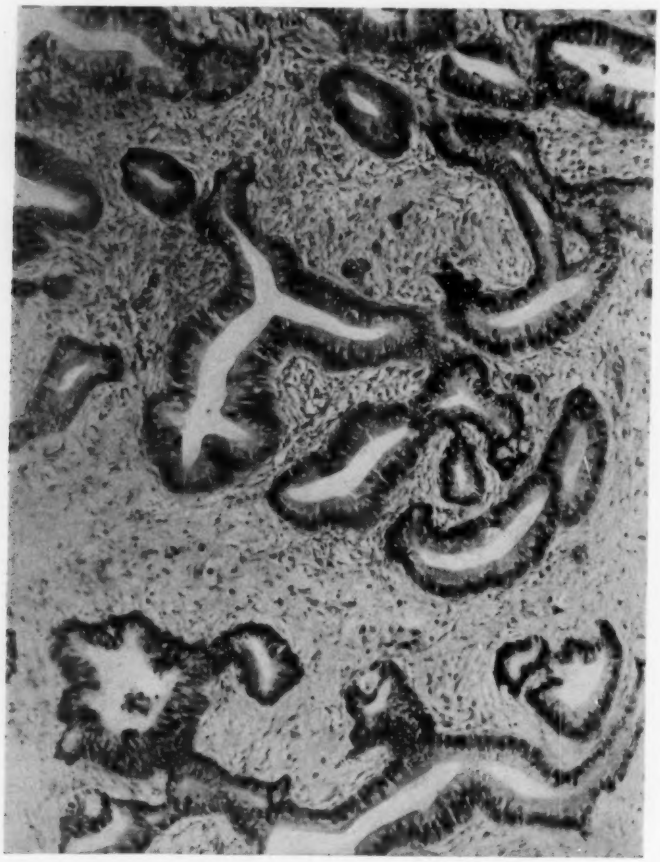

FIG. 8.—Carcinoma of the colon with slight loss in polarity of the cell nuclei. (×200)

large areas of the tumor, sometimes to such a degree that the epithelial elements were difficult to find. The difference is apparently mainly one of degree. The excess "colloid" can even be recognized in the gross specimen. Seven of the 15 cases were of the signet-ring cell type. Most pathologists regard them as a particularly malignant group and often class them separately. Just how these two types should be grouped is still an undecided question. The distinction between them is not always clear-cut. Intermediate types are not infrequent. They may occupy scattered areas in a tumor which presents, in its other portions, a typical adenomatous structure without excess "colloid." They may be associated with each other so that "colloid" areas with well differ-

entiated glands mingle with signet-ring cells which have usually lost their glandular arrangement. Classification in these cases is difficult.

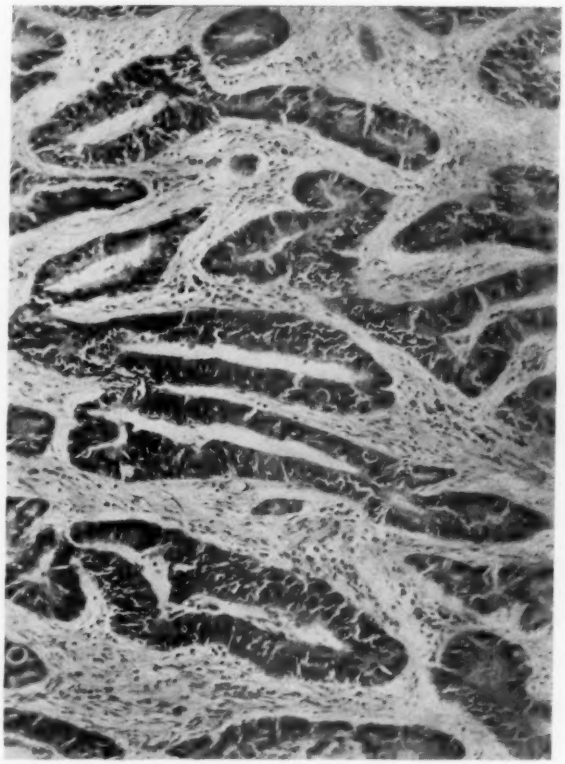

FIG. 9.—Carcinoma of the colon with moderate loss in polarity of the cell nuclei. (×200)

Our follow-up results with reference to the "mucin" content of the tumors were quite inconclusive, irrespective of whether the signet-ring group was included or not. This criterion was, therefore, not used in grading.

TABLE V

EXTRACELLULAR "MUCOID" MATERIAL

Signet-Ring Cells Included

		Slight	*Moderate*	*Marked*
Cases	126	94	15	17
Five-year survivors:				
Cases	68	50	9	9
Per cent	54%	53%	60%	53%
Five-year survivors without evidence of disease:				
Cases	61	45	8	8
Per cent	48%	48%	53%	47%

Size of Nuclei and Variation in Size of Nuclei.—The average size of the nuclei and the variation in size of the nuclei were discarded as reliable criteria

because of the difficulty in getting accurate measurements and of getting an accurate average figure for the nuclear diameter, even with the help of an

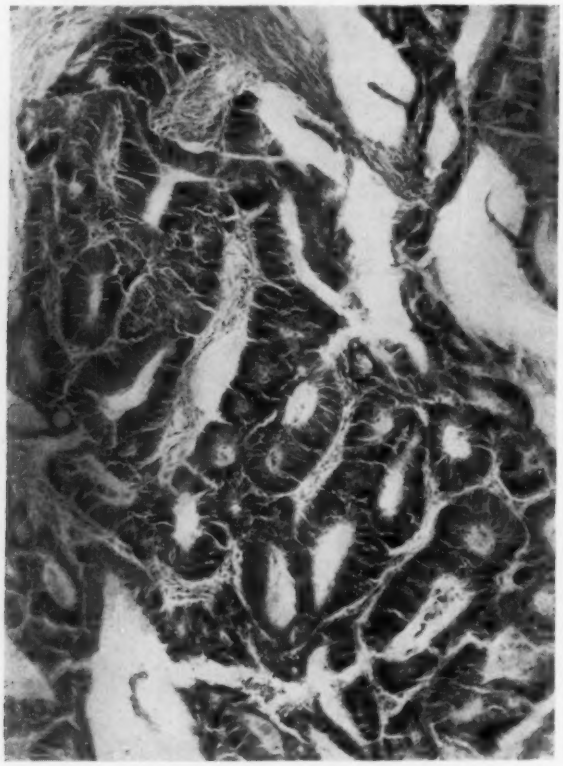

FIG. 10.—Carcinoma of the colon with marked loss in polarity of the cell nuclei. (×200)

eye-piece micrometer. Variations in fixing and staining technic also tend to make this method unreliable.

TABLE VI

NUMBER OF MITOSES

		Few (Less than 1)	*Moderate* (1 or 2)	*Numerous* (Over 2)
Cases	126	19	70	37
Five-year survivors:				
Cases	68	15	36	17
Per cent	54%	79%	51%	46%
Five-year survivors without evidence of disease:				
Cases	61	14	32	15
Per cent	48%	74%	46%	41%

Number of Mitoses.—The frequency of mitoses has always been considered one of the best means of judging the cellular activity of a tumor.

It was accepted for purposes of grading although the results were not particularly convincing. It is realized that of all the criteria adopted this one lends itself most of all to technical errors because of variations in staining and fixing technic. It was the least convincing of the criteria chosen.

The above results, obtained in testing the various criteria, were nearly

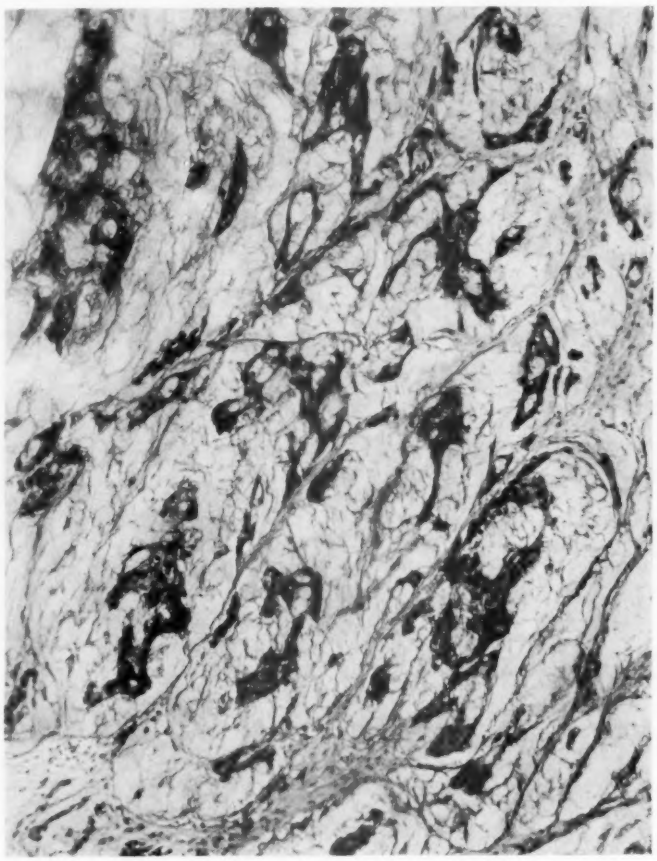

FIG. 11.—"Mucoid" or "colloid" carcinoma of the rectum not of the signet-ring cell type. (×200)

the same, whether computed separately for the right colon, left colon, rectum, or for all combined.

METHOD OF GRADING.—Three grades of malignancy were adopted for this series of cases instead of four as used by Broders,[14] and Stewart and Spies.[7] We agree with Haagensen that, in the present state of our knowledge, the interpretation of differences in histologic structure is not sufficiently accurate to warrant more than a very simple classification.

On the basis of the results, four histologic criteria were chosen for grading. They were the invasive tendency, glandular arrangement, nuclear polarity, and frequency of mitoses.

As shown in the preceding tables, each criterion was subdivided into three groups. In order to work out a tentative numerical method of grading, each group was rated one, two, or three points, according to the degree the characteristic was present. The lowest possible total for a tumor judged by these four criteria was, therefore, four, and the highest, 12. The three grades were then arbitrarily divided according to points as follows: Grade I, 4–6 points (inclusive); Grade II, 7–8 points (inclusive); and Grade III, 9 points and

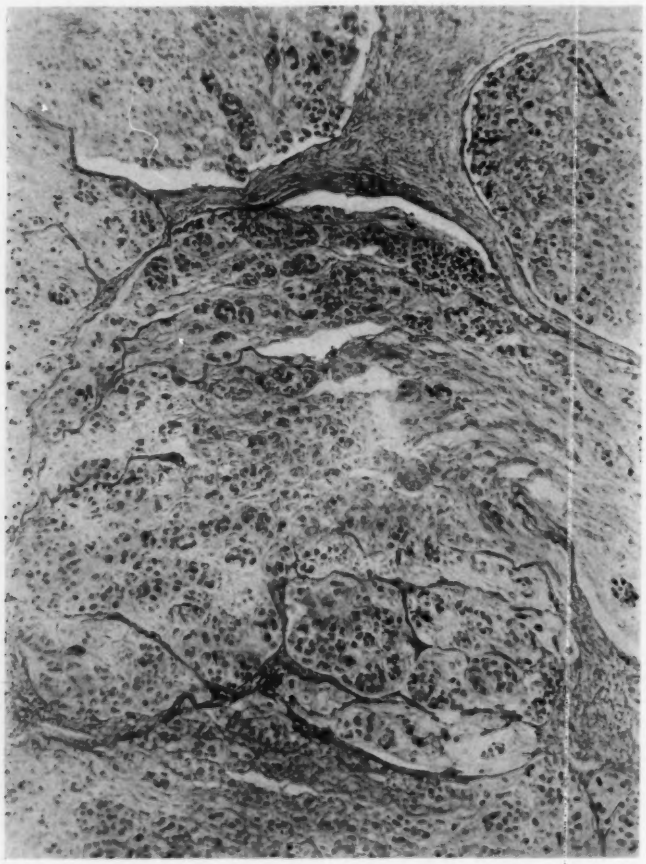

FIG. 12.—"Mucoid" or "colloid" carcinoma of the colon of the signet-ring cell type. (×33)

over. This method has been referred to in a later table as the numerical method of grading.

There are several objections to such a method. It tends to become too rigid and complicated. The attempt at mathematical accuracy is out of proportion to our ability to rate histologic characteristics correctly. Moreover, it places an equal value on each criterion which is probably incorrect. Realizing the shortcomings of such a method, the cases were also graded on the basis of these four criteria but without any attempt at numerical evaluation.

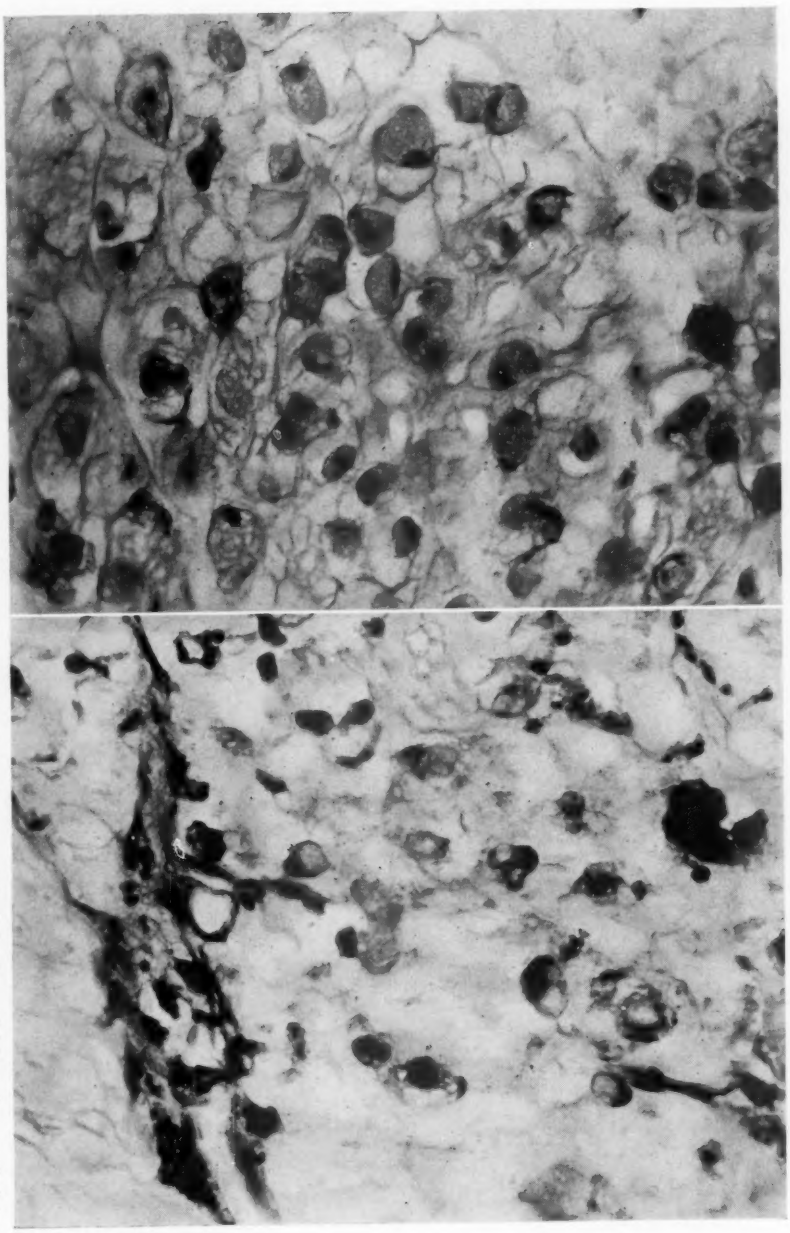

FIG. 13.—"Mucoid" or "colloid" carcinoma of the colon of the signet-ring cell type. In the area at the left, the nuclei have been pushed to one side of the cell but have not become flattened. In the area at the right, the cells show the more typical signet-ring appearance. (×400)

This method has been referred to in a later table as the nonnumerical method. It may increase the human factor in grading, but has the advantage of simplicity and gives the pathologist more leeway in judging the relative importance of the criteria. It was noted that with this method the tendency was to put greater emphasis on the manner of growth of the tumor, especially as to invasiveness, than on the frequency of mitoses. That such an emphasis may be warranted is suggested by the fact that invasiveness was shown by follow-up results to be apparently of more value in prognosis than any of the other

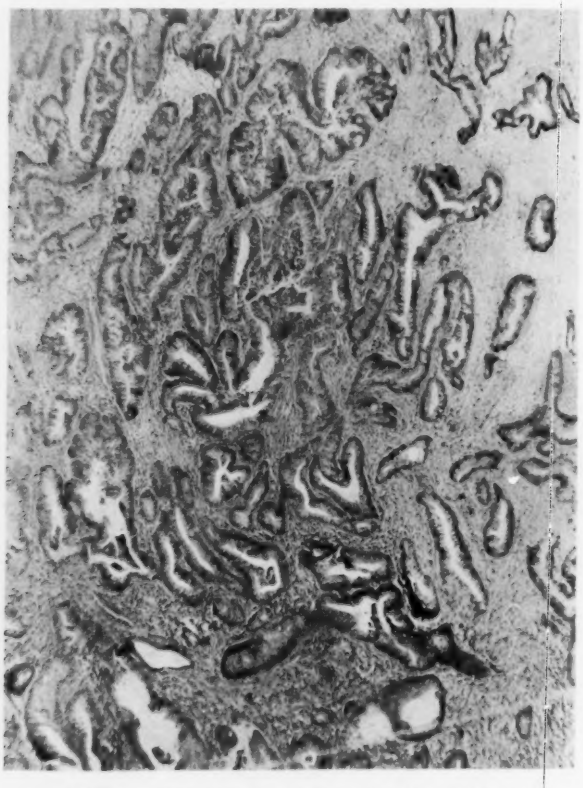

FIG. 14.—Carcinoma of the colon, Grade I. (×85)

criteria. Grading was estimated mainly with the low power magnification (x80), except in determining the frequency of mitoses. In comparing the grades adopted under these two methods, surprisingly little difference was found. Accordingly, the simpler nonnumerical method was chosen as preferable and has been used throughout this analysis. Whichever method is used, the general characteristics of a tumor belonging to each grade is the same.

Grade I.—Tumors of this grade show a well differentiated, compact glandular structure. The acini are lined with two or three layers of cells whose nuclei tend to remain close to the basal layer of the gland, leaving a clear zone near the lumen. There is little tendency of individual cells or small

groups of cells to push out into the surrounding tissue. Mitoses are infrequent. Although our results did not give definite data on papillary structure, we believe many tumors in this grade show a close resemblance to the benign adenoma.

Grade II.—In this grade, the glandular arrangement is still preserved. Some glands, however, appear to be loosely and irregularly arranged. Their walls are thicker and are composed of cells in three or more layers with their

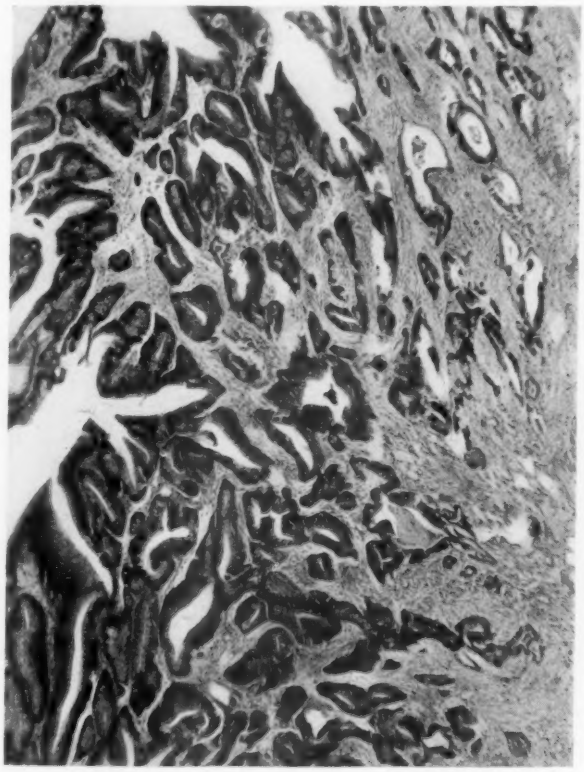

FIG. 15.—Carcinoma of the colon, Grade II. (×85)

nuclei scattered throughout the wall of the gland. The central clear zone in the cytoplasm of the cells about the lumen is largely lost. A tendency of the cells to stray off into the tissues can be seen, especially at the deep advancing edge of the tumor. Mitoses are more numerous.

Grade III.—The glandular structure may be completely or nearly completely lost. Parts of the growth, at least, may show tumor cells growing in solid masses or cords with little tendency to arrange themselves around a central lumen. Individual cells or small clumps may be seen streaming out irregularly into the tissues. This is again usually most marked at the deep edge of the tumor. Nearly all cell polarity is lost. Mitoses are frequent.

When the tumor shows considerable morphologic variations in different

areas, and this was not infrequent, grading may be difficult. In this event, the grade of the tumor was taken as that of the least differentiated area.

"Mucoid" or "colloid" tumors, whether of the signet-ring cell type or not, were graded by the same criteria as the other tumors, and were not arbitrarily placed in any one grade.

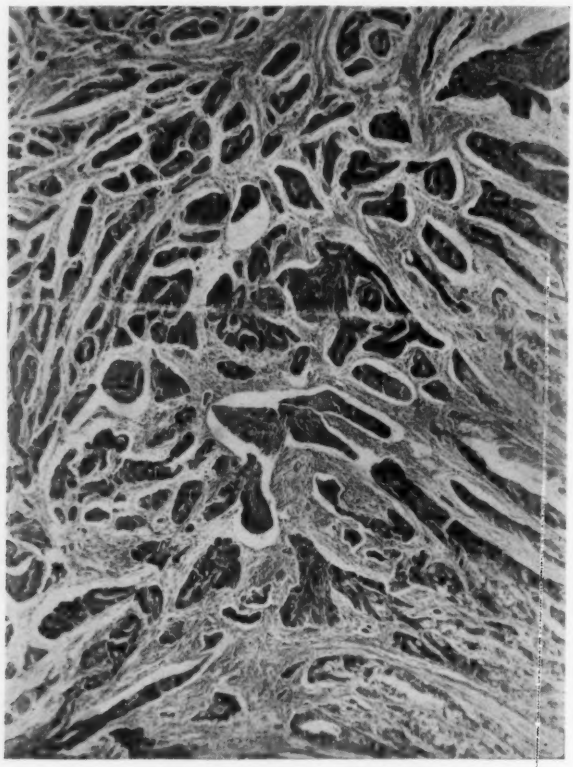

FIG. 16.—Carcinoma of the colon, Grade III. (×85)

DISTRIBUTION OF CASES IN GRADES.—The distribution of cases in the three grades showed that most were in Grade I and Grade II, emphasizing the relatively good differentiation of most of these tumors. The proportion of cases in the grades was approximately the same, whether calculated only for the five-year survivors with or without the disease and those dead from recurrences, or for the entire group irrespective of follow-up results. The latter group is shown in Table VII because of its larger size. The distribution in the colon and rectum was similar but showed several marked differences. The incidence of Grade I cases was 19 per cent higher, and that of Grade III cases 16 per cent lower, in the colon than in the rectum, suggesting that colon tumors tend to be better differentiated.

There were 27 "mucoid" or "colloid" tumors, 13 per cent of the whole series. The incidence was about the same in the right and left colon and rectum. Rankin and Chumley found an incidence of 4.9 per cent, and Parham

of 16 per cent, in the colon and rectum combined. Ten of the 27 cases were of the signet-ring type, and 17 were not. When the 17 "colloid" cases, exclusive of the signet-ring type, were studied separately, they were found to show by far the greater proportion of cases in Grade I, with a 21 per cent higher figure than that for the whole series. All but two of the 10 signet-ring tumors, on the other hand, were in Grade III, with none in Grade I. Ochsenhirt,

TABLE VII

DISTRIBUTION OF CASES ACCORDING TO GRADE

	Grade I	*Grade II*	*Grade III*
Right colon:			
Cases	12	11	5
Per cent	43%	39%	18%
Left colon:			
Cases	40	26	12
Per cent	51%	33%	15%
Right and left colon:			
Cases	52	37	17
Per cent	49%	35%	16%
Rectum:			
Cases	33	42	35
Per cent	30%	38%	32%
Colon and rectum:			
Cases	85	79	52
Per cent	39%	37%	24%

Raiford, Wood and Wilkie, and Rankin and Chumley had similar findings and stressed the greater malignancy of the signet-ring tumors. It should be emphasized again that grading "colloid" tumors was often difficult because of the scarcity of epithelial cells. Most of the signet-ring cases were in the rectum and most of the other "colloid" cases in the colon.

TABLE VIII

FOLLOW-UP RESULTS ACCORDING TO GRADE

Nonnumerical and Numerical Methods

		Grade I		*Grade II*		*Grade III*	
		Nonnumerical	Numerical	Nonnumerical	Numerical	Nonnumerical	Numerical
Cases	126	46	50	45	40	35	36
Five-year survivors:							
Cases	68	37	38	21	19	10	11
Per cent	54%	80%	76%	47%	48%	29%	31%
Five-year survivors without evidence of disease:							
Cases	61	32	33	21	19	8	9
Per cent	48%	70%	66%	47%	48%	23%	25%

FOLLOW-UP RESULTS ACCORDING TO GRADE.—The follow-up results showed a marked difference in the chances of survival in the three grades. The incidence of Grade I cases surviving operation for five years without evidence of the disease was over three times that of the Grade III cases, and 23 per cent more than for the Grade II cases. The correlation between grades and survival was about the same in both the colon and rectum. It should be reemphasized that these results are based only on five-year survivals with or without disease, and those dead from recurrences. Operative deaths and those dying from other causes have not been included here. The results by both the nonnumerical and numerical methods are given below. As we have already explained, they were nearly the same in each case. The nonnumerical method was adopted because of greater simplicity.

The value of grading was then studied in the cases without and with metastases in the lymph nodes. As would be expected, the cases without node involvement gave much better results than those with involvement. The influence of the grades on the results was shown in both groups. It appeared to be greater in cases with node involvement, although this group is presumably more affected by the extent of the disease at the time of operation. Rankin and Olson found that the grades influenced prognosis about equally in both these groups.

TABLE IX

FOLLOW-UP RESULTS ACCORDING TO GRADE

In Cases With and Without Lymph Node Metastases

	Grade I		*Grade II*		*Grade III*	
	Node Metastases		Node Metastases		Node Metastases	
	Absent	Present	Absent	Present	Absent	Present
Cases	44	2	29	16	13	22
Five-year survivors:						
Cases	36	1	15	6	8	2
Per cent	82%	50%	52%	37%	62%	9%
Five-year survivors without evidence of disease:						
Cases	31	1	15	6	6	2
Per cent	70%	50%	52%	37%	46%	9%

The relationship between the grade of the tumor and the incidence of node metastases was also studied and is shown in the following table. Grade III cases had an incidence nine times greater than Grade I. Rankin and Olson, and Wood and Wilkie had similar findings.

TABLE X

INCIDENCE OF NODE METASTASES ACCORDING TO THE GRADE

	Grade I	*Grade II*	*Grade III*
Cases	85	79	52
Cases with node metastases	5	25	28
Per cent of cases with node metastases	6%	32%	54%

As grading is primarily a measure of the rapidity of growth, its influence should be seen in comparing the duration of life after operation in those dying with recurrences. Grade I cases had an average postoperative life of 34 months, as compared to 22 months in both Grades II and III, a difference of just a year. No difference was found between the Grade II and III cases. The number of cases, however, is too small to warrant definite conclusions.

DUKES' METHOD OF PROGNOSIS ACCORDING TO THE EXTENT OF SPREAD.—From the previous tables it would seem evident that the grade of a tumor is a determining factor in the patient's prognosis. There is, however, another factor of even greater importance, and that is the extent of spread of the tumor. Obviously, the knowledge that a tumor was incompletely removed at operation or that it proved to be confined to the mucosal layer is of greater prognostic value to the surgeon in any specific case than its histologic characteristics. Dukes[5] has adopted a classification based on the extent of spread which should be studied before the relative merits of the two methods can be judged.

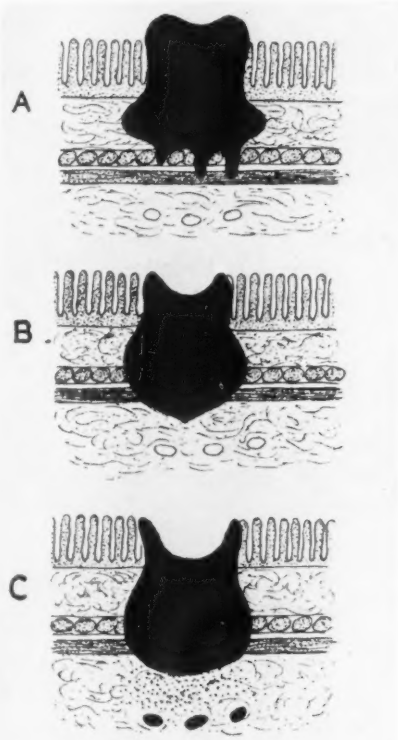

FIG. 17.—Dukes' classification of carcinoma of the rectum (after Dukes).

Dukes divided cancers of the rectum into three groups, A, B, and C: (A) Cases in which the growth was confined to the wall of the rectum. (B) Cases which had spread by direct continuity to the extrarectal tissues but had not reached the regional lymph nodes. (C) Cases which had metastases in the regional nodes. He showed that lymphatic metastases rarely occurred until the growth had penetrated the muscle layers into the extrarectal tissues and become a B case. None of his cases with the tumor limited to the rectal wall had node involvement. Miles[21] has reported several exceptions to this rule, and Wood and Wilkie[8] had two out of 100 rectal carcinomata studied, but they are apparently very rare.

The classification of our colon and rectal cases by Dukes' method showed that the greater number were B cases, with a smaller, but nearly equal, number of A and C cases. The percentage of advanced C cases in the rectum was

twice as great as in the colon. Conversely, there was only 18 per cent of the rectal tumors in the A group, as compared to 34 per cent of the colon tumors. The proportion of tumors in an early A stage was especially high in the right colon, 44 per cent. Apparently, cancers of the rectum were operated upon at a later stage in their development than those in the colon. Whether this difference was due to the more rapid spread of the rectal growths, to delay in operation, or to the late development of symptoms in these cases was not determined. A comparison of our rectal cases with the series reported by Dukes showed a similar distribution except for a 10 per cent higher proportion of C cases in his series. This difference may be due to the fact that in our earlier cases the gross and microscopic examination of the lymph nodes was less carefully made than in our later cases, and was sometimes inadequate.

TABLE XI

DISTRIBUTION OF CASES ACCORDING TO DUKES' CLASSIFICATION

	A	*B*	*C*
Right colon:			
Cases	12	11	4
Per cent	44%	41%	15%
Left colon:			
Cases	24	40	14
Per cent	31%	51%	18%
Right and left colon:			
Cases	36	51	18
Per cent	34%	49%	17%
Rectum:			
Cases	20	49	40
Per cent	18%	45%	37%
Colon and rectum:			
Cases	56	100	58
Per cent	26%	47%	27%

Our series has upheld Dukes' contention that extension of the tumor through the rectal wall is by continuity and that only when the tissues outside of the wall are reached do metastases to the nodes occur. Of 69 colon and rectum tumors with node metastases studied microscopically, only two showed the nodes involved before the smooth muscle layers of the bowel wall had been penetrated. Both were in the rectum. One of the cases was particularly unusual. The growth was limited entirely to the mucous layer of the bowel. At one point the muscularis mucosae appeared to be interrupted, but the submucosa was not invaded in the sections studied. One node, however, showed metastasis. There were four other cases which at first appeared to be exceptions to this rule, but which were later found to follow it after new sections had been made and studied. Our series has also shown that Dukes' generalization is true, except for rare exceptions, not only for the rectum but for the colon as well. Once the tumor had penetrated the muscle layers, however, and invaded the extrarectal tissues, node involvement was found in 26 per cent of the colon cases and 45 per cent of the rectal cases.

If the 10 signet-ring tumors are taken separately, they all proved to be cases. On the other hand, the 17 other "colloid" cases showed about the same distribution in each group as did the whole series.

THE VALUE OF DUKES' CLASSIFICATION IN PROGNOSIS.—The five-year follow-up showed strikingly different results in the A, B, and C cases. As in previous tables, they were based only on cases surviving operation five years with or without disease, and those dying from cancer within that period. The A, B, and C, groups had 100, 43, and 23 per cent five-year survivors, respectively, without evidence of disease in the colon and rectum combined. Thus, the chances of being alive over five years was over four times as good for the A as for the C cases. The results were approximately the same in the colon and rectum separately as in the combined group. No A case, definitely proven by gross and microscopic examination, has died after operation from the disease. There were several cases, however, which were difficult to classify as A or B cases because of inadequate sections. For proper accuracy, such a classification requires that sections be taken at the point of deepest penetration of the growth. Repeated sections may be necessary to determine whether or not it has spread beyond the bowel wall. Not all of our sections in the early cases completely met these requirements. These results are very similar to those reported by Dukes[6] for a series of 128 carcinomata of the rectum treated by perineal excision. He had 93, 65, and 23 per cent five-year survivors in the A, B, and C cases. Gordon-Watson[22] has suggested that the difference between the five-year survival rates of the A and B cases after operation may be partly explained by the greater liability of the B cases to spread by venous channels. He points out, however, that invasion of the veins with metastasis to the liver before the lymph nodes are involved is rare.

TABLE XII

FOLLOW-UP RESULTS ACCORDING TO DUKES' CLASSIFICATION

		A	*B*	*C*
Cases	124	27	58	39
Five-year survivors:				
Cases	68	27	32	9
Per cent	54%	100%	55%	23%
Five-year survivors without evidence of disease:				
Cases	61	27	25	9
Per cent	49%	100%	43%	23%

The value of this classification in prognosis is obvious. It shows the great importance of determining the exact extent to which the bowel wall has been penetrated and whether or not the nodes contain metastases. The difference in survival in the three groups was even more clear-cut than that seen when the results in the three histologic grades were compared. It is unfortunate

that the B group with indeterminate prognosis was so large and contained 47 per cent of the cases.

Before comparing the value of the two methods, however, the distribution of the A, B, and C cases in the three histologic grades, I, II, and III, should

TABLE XIII

DISTRIBUTION OF GRADES ACCORDING TO DUKES' CLASSIFICATION

	A	*B*	*C*
Grade I:			
Cases	39	39	6
Per cent	46%	46%	7%
Grade II:			
Cases	14	38	24
Per cent	19%	50%	31%
Grade III:			
Cases	4	19	28
Per cent	8%	37%	55%

be studied. Table XIII shows a definite relationship between the two classifications. There is a high proportion of A cases in Grade I, and a very low proportion in Grade III, whereas the C cases with lymph node metastases are most numerous in Grade III and fewest in Grade I. This relationship is seen in the colon and rectal group separately as well as in the combined group. Dukes[6] found this same correlation between the two classifications in his series.

Dukes has suggested that the apparent value of histologic grading is misleading. He believes that much of its significance can be attributed to this distribution of early A cases in Grade I and of late C cases with node metastases in Grade III, rather than to the histology of the tumor itself. But these differences in the limits of spread of the tumors in the grades must be due to differences in their rate of growth or, in other words, to the grade of malignancy. The two classifications are closely related. The extent of spread is based primarily on the activity and grade of the tumor. It is more important than the grade in any individual case. Unfortunately, it cannot always be determined with absolute accuracy. If it could be so determined, the prognosis would be easy except in the C cases. Nearly every A and B case would be assured of cure, and only the C cases would be left in doubt. But the limits of growth can only be gauged approximately. Errors are unavoidable. Grading gives further information on which to estimate the probable extent of the tumor in both the early and late cases. It is perhaps of most value when applied to a group of tumors. As Dukes has remarked, it is essentially an index of the "pace of growth." The two methods should be used to supplement one another. They give different kinds of information, both of which are helpful in prognosis.

An attempt has been made to combine the two methods in a common classification. The five-year results were studied in each of the nine possible combinations, as shown in Table XIV. The classification is somewhat compli-

cated but seems to show promise, as the results indicate. The Dukes' rating is placed before that of the grade as it is the more important of the two. The number of cases is as yet too small to test the real value of the method in prognosis.

TABLE XIV

FOLLOW-UP RESULTS ACCORDING TO GRADE AND DUKES' CLASSIFICATION COMBINED

	A1	*A2*	*A3*	*B1*	*B2*	*B3*	*C1*	*C2*	*C3*
Cases	18	6	2	25	22	11	2	16	22
Five-year survivors:									
Cases	18	6	2	18	9	6	0	6	3
Per cent	100%	100%	100%	72%	41%	55%	—	38%	14%
Five-year survivors without evidence of disease:									
Cases	18	6	2	13	9	4	0	6	3
Per cent	100%	100%	100%	52%	41%	36%	—	38%	14

LYMPH NODE METASTASES AND PROGNOSIS.—The presence or absence of lymph node metastases has often been used as a rough basis for prognosis. Such a method is somewhat similar to Dukes' but less accurate. The incidence of node metastases has been shown to be 27 per cent for all the cases in the series. It was twice as high in the rectum as in the colon. This figure is probably considerably lower than it should be, as the earlier cases in the series were not examined as thoroughly as the more recent ones. In a recent carefully examined series of 100 rectal cases treated by perineal and perineoabdominal excision, Gabriel, Dukes and Bussey[23] found node metastases in 62 per cent. Wood and Wilkie[8] found them in 51 per cent of cases in a similar series. The incidence of node metastases was 30 per cent for the 27 "colloid" cases in our series. In the 10 "colloid" cases of the signet-ring type it was 50 per cent, and in the 17 other "colloid" cases 18 per cent. Rankin and Chumley[16] found node involvement in 58 per cent of all their "colloid" cases.

TABLE XV

INCIDENCE OF LYMPH NODE METASTASES

	Right Colon	*Left Colon*	*Right and Left Colon*	*Rectum*	*Colon and Rectum*
Total cases	27	78	105	107	212
Cases with node metastases	4	15	19	39	58
Percentage of cases with node metastases	15%	19%	18%	36%	27%

It has already been shown that cases with node metastases usually belong to a more malignant grade. Sixty per cent of cases with node metastases were in Grade III as compared to only 4 per cent in Grade I. A comparison of the follow-up results showed 60 per cent of the cases without metastases, and 23 per cent of those with metastases alive five years without the disease,

making the incidence of survival two and one-half times higher in the former group. The results were based on cases dead from the disease or alive five years with or without it.

Classification of Tumors as Projecting, Intermediate and Infiltrating, for Prognosis.—The tendency of a tumor to grow out into the lumen of the bowel or to infiltrate into the surrounding tissues has often been used as a guide to prognosis not only in the large intestine but in other parts of the gastro-intestinal tract. Whipple and Raiford[24] have recently emphasized its use in cancer of the stomach. On the other hand, Dukes[25] believes that such a classification of rectal cancer is misleading, and that these characteristics are simply stages in the life history of the tumor and do not represent different types. He believes that the growth at first projects into the lumen, perhaps arising from a benign adenoma, and that later as it increases in size its projecting portion with a poorer blood supply and greater exposure to infection sloughs away leaving an infiltrating ulcer. It is probable that this sequence sometimes occurs, but that it accounts for the differences in gross pathology in most cases seems doubtful. In our series, the tumors were divided into three groups, projecting, intermediate, and infiltrating. Only cases with gross specimens available for examination were included. The proportion of cases in each group was 29, 49, and 22 per cent, respectively. On comparing the histologic grades of these tumors, the projecting type proved to be mostly Grade I, and the infiltrating Grade III. This is what might be expected, and gives further evidence of the benign character of the projecting tumors as compared with the infiltrating.

The five-year results were far better in the projecting than in the infiltrating cases, as might be expected. This was true both in the colon and rectum. Rankin and Olson[4] reached a similar conclusion from a study of colon carcinomata.

Table XVI

FOLLOW-UP RESULTS IN PROJECTING, INTERMEDIATE AND INFILTRATING TUMORS

		Projecting	*Intermediate*	*Infiltrating*
Cases	81	23	42	16
Five-year survivors:				
Cases	44	19	19	6
Per cent	54%	83%	45%	38%
Five-year survivors without evidence of disease:				
Cases	40	18	19	3
Per cent	49%	78%	45%	19%

This classification is of some value in prognosis. It is similar to that of Dukes but less accurate. The distinction between the three groups is often difficult to make and at best is only approximate.

Regional Variations in Grade.—Variations in morphology in different parts of the tumor are frequent in cancer of the colon and rectum. For this

reason, microscopic sections from several areas should always be taken. It is especially important to study the deep infiltrating edge which is often the least differentiated. In about 15 per cent of the cases in this series, such variation made grading difficult. The grade of the more anaplastic of the two areas was usually taken as the grade for the tumor itself. In general, however, the same grade was found throughout the tumor.

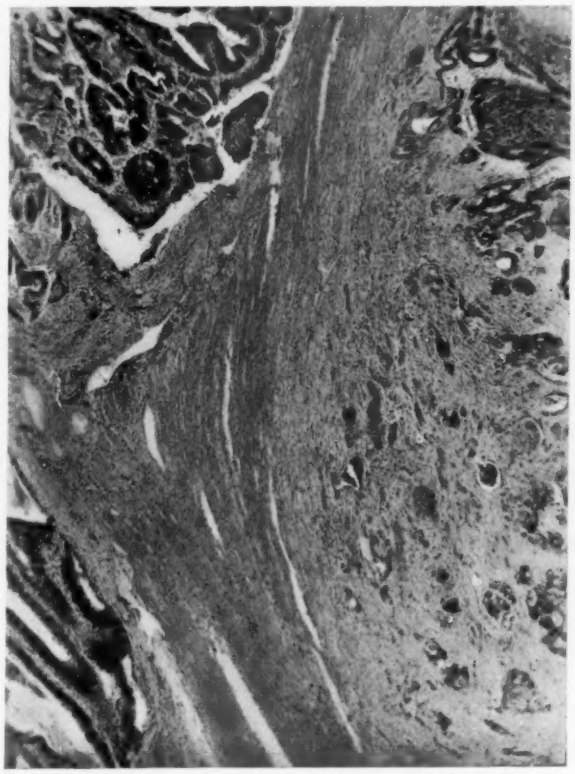

FIG. 18.—Carcinoma of the rectum showing marked variation in morphology and grade in the same tumor. (×85)

The relation of the grade of the tumor and that of the metastases in the regional nodes was also studied. All cases were included irrespective of follow-up. There were 62 in all. In 53, or 85 per cent, the grade was the same. In three, or 5 per cent, the grade in the nodes was more malignant than in the parent tumor, and in six cases, or 10 per cent, it was less malignant. That the grade is usually maintained in the metastases, and if changed is as often of a higher as of a lower grade was noted by Gates and Warren,[26] and Mills, Broders, and Caylor[27] in various types of carcinomata, and by Haagensen[11] in cancers of the breast.

COMPARISON OF THE GRADE OF BIOPSIES AND OF THE PARENT TUMOR.—It has long been recognized that biopsies may fail to give a correct picture of the histology of a tumor. The specimen is often too small for adequate

study. It only includes one area of the tumor, is usually taken from the surface of the growth, and does not include the deep edge which is often the least differentiated. These disadvantages are encountered particularly in judging the invasive tendency of the growth, which has been shown to be one of the most important criteria in grading. In 20 consecutive biopsies, Dukes found that the biopsy showed a lower grade than the main tumor in 16. He considered them unsatisfactory for grading. On the other hand, Stewart and Spies studied a series of carcinomata of the rectum based entirely on biopsies. Although admitting their limitations, they believe that they are adequate for grading and are of definite value in prognosis.

In our series there were 74 cases of cancer of the rectum and rectosigmoid in which biopsies wre taken and could be compared with sections from the tumor after removal. In 58, or 78 per cent of the 74 cases, the biopsy was of the same grade as that of the tumor on later examination. In 10 of these cases, the biopsy appeared somewhat less malignant than the tumor, but not enough to receive a different grade. In 16 cases, or 22 per cent, the biopsy was at least one grade less malignant than the tumor was rated, and in two cases there was a difference of two grades, the biopsy being Grade I and the tumor Grade III. There were no cases in which the biopsy appeared to be more malignant than the tumor itself. In addition, it may even fail to give the correct diagnosis. A diagnosis of benign adenoma was made from the biopsy in several cases in our series only to be disproved on later examination.

The Size of Lymph Nodes and Metastases.—It is often difficult to determine at operation whether or not the regional nodes are involved. The size of the nodes has not proved to be a reliable guide. Enlargement is often due to inflammation rather than to metastases. In this series, there were 97 cases with nodes reported to be enlarged at operation or in the pathologic examination of the gross specimens. Of these, 62 per cent proved to be uninvolved with only 38 per cent showing metastases. Of the nodes that showed metastases, only about one-half were reported enlarged. In the colon alone the size of the nodes proved even more misleading. Only 21 per cent of the nodes reported enlarged were positive.

Annularity.—In over one-half of the cases in the series, or 57 per cent, in which gross specimens were available for study, the growth completely encircled the bowel. This was over twice as frequent in the colon as in the rectum, 78 per cent as compared to 34 per cent. No special relationship was found between the grade of the tumor and the prevalence of complete annularity. The five-year results were considerably better when the tumor was not completely annular than when it was, as might be expected. The incidence of five-year survival without disease was 59 per cent in the former group, and 40 per cent in the latter. The results did not include the operative deaths, those lost to follow-up, and those dead from other causes.

Age.—Age has long been thought to be an important factor in prognosis. Cancer of the colon and rectum in the younger age groups is generally believed to give a poorer outlook. Rankin and Comfort[28] found a greater proportion

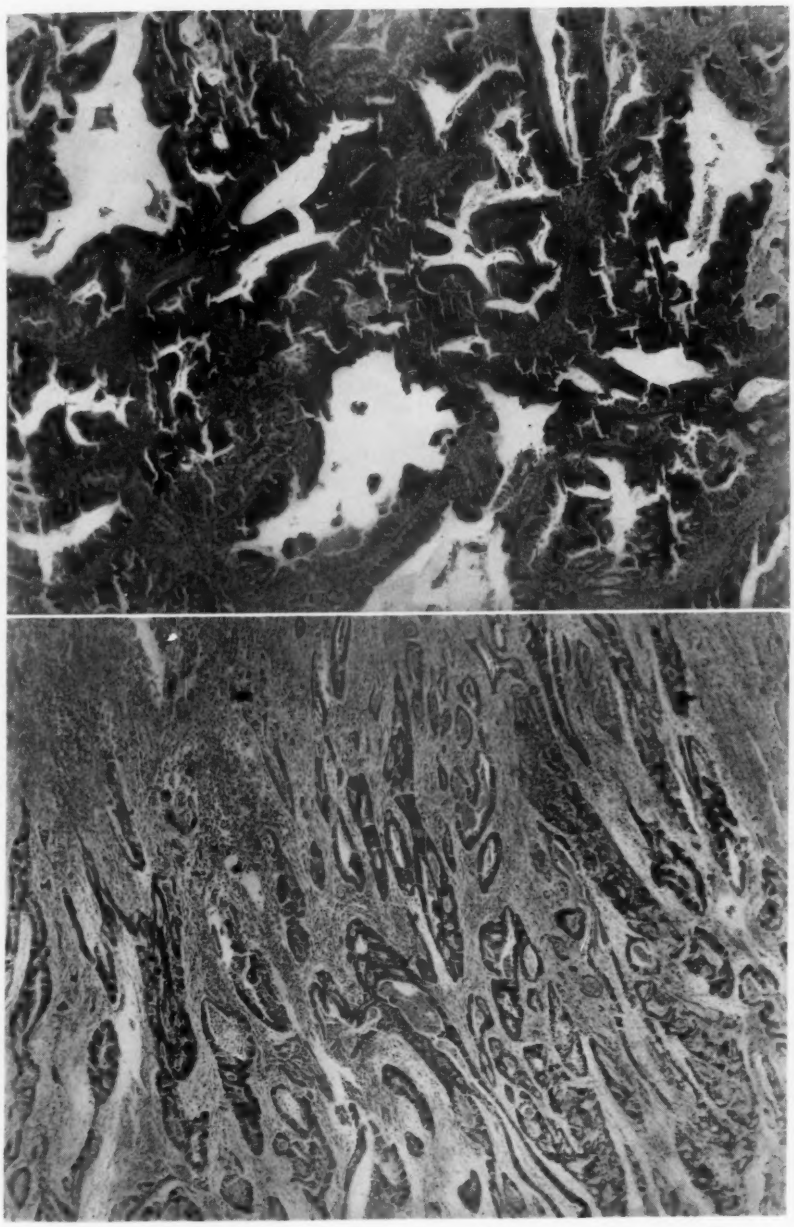

FIG. 19.—Carcinoma of the rectum showing biopsy: Grade I, on the left, and on the right, section from the tumor taken after operation, Grade III. (×85)

of higher grade tumors and poorer five-year results in patients age 30 years and less. Shedden[29] also concluded that the grade decreases as the age increases. Stewart and Spies[7] found the average age somewhat less in the most malignant grade in a small series of rectal carcinomata. Gates and Warren,[26] on the other hand, found the relative frequency of the grades to be the same in each age group in a large series of epidermoid cancers. In this series no relationship could be shown between the grade of malignancy and the age of the patient. The results in the different decades were also compared. No definite difference could be demonstrated, however. It is true that between 20 and 29 years of age the five-year survival incidence was only 17 per cent, as compared to a general average of 32 per cent, but there were only six cases in this group.

The average age of both the colon and rectal cases at operation was 52 years. In the right colon cases it was 49 years, slightly less than in the left colon or rectum cases. Most cases occurred in the fifth and sixth decades. The youngest patient was 28, and the oldest 77 years old.

TABLE XVII

FOLLOW-UP RESULTS IN THE DIFFERENT AGE GROUPS

		20–29	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*
Dead of disease or living five years with or without disease	126	4	22	28	40	32	0
Operative deaths	61	2	6	13	21	15	4
Lost to follow-up	18	0	2	3	7	5	1
Dead under five years from other causes	7	0	0	1	1	5	0
Total cases	212	6	30	45	69	57	5
Five-year survivors:							
Cases	68	1	12	15	23	17	0
Per cent	32%	17%	40%	33%	33%	30%	—
Five-year survivors without evidence of disease:							
Cases	61	1	12	13	22	13	0
Per cent	29%	17%	40%	29%	32%	23%	—

PROGNOSIS BEFORE OPERATION.—The foregoing discussion has been confined chiefly to determining prognosis after operation when complete gross and microscopic specimens are available. Of even greater interest to the surgeon is prognosis before operation. Unfortunately, this is much more difficult. It is only possible to any degree in rectal tumors that can be palpated or seen with the proctoscope and from which biopsies can be obtained. The most important factor in prognosis, the extent of spread of the growth, cannot be accurately determined at this time. The early A cases can perhaps be identified by their mobility, small extent, and tendency to project into the lumen. The more advanced tumors may be suspected by their fixation, greater

degree of annularity, ulceration, and extent. Except in certain extreme cases, however, size is not a reliable criterion of operability. Moreover, as Westhues[30] has pointed out, fixation to the sacrum or prostate is more often due to inflammatory reaction than to carcinoma. Mesenteric node involvement can seldom be determined before operation. Westhues has also asserted that there is little relationship between the extent of the growth locally and the presence of liver metastases. The histologic grade of the tumor obtained by biopsy is an important aid in prognosis, but indicates only the probabilities of the extent of the growth. Biopsy, moreover, is not always reliable and in nearly one-fourth of our cases was one grade less malignant than the true grade of the tumor. It should be used with great caution in determining operability in any individual case. Thus, even with all the means available, the accurate prognosis of rectal tumors before operation is not yet possible.

Follow-up Results.—In presenting the results of surgical treatment, the operative deaths, the cases lost to follow-up, and those dying under five years from other causes should be included. Otherwise, the results are misleading and present too favorable a prognosis. The inclusion of these cases, for example, brought down our five-year results without evidence of disease from 48 to 29 per cent for the colon and rectum. Tables XVIII and XIX have been prepared, however, for comparison with other series of cases calculated on similar bases. The results in the colon were better than in the rectum, 32 per cent as compared to 25 per cent. The right colon showed the best percentage of all, 37 per cent. Rankin and Olson also had a somewhat better five-year follow-up in the right colon cases as compared to the left, but could give no explanation for the difference. The poorer result in the rectum is in keeping with our previous finding that rectal tumors show a higher propor-

Table XVIII

FOLLOW-UP RESULTS

Operative Deaths, Cases Lost to Follow-Up, and Cases Dead from Other Causes Included

	Right Colon	*Left Colon*	*Right and Left Colon*	*Rectum*	*Colon and Rectum*
Cases dead of disease or alive five years with or without disease	14	48	62	64	126
Operative deaths	9	19	28	31	59
Lost to follow-up	2	10	12	6	18
Dead under five years from other causes	2	1	3	6	9
Total cases	27	78	105	107	212
Five-year survivors:					
Cases	10	26	36	32	68
Per cent	37%	33%	34%	30%	32%
Five-year survivors without evidence of disease:					
Cases	10	24	34	27	61
Per cent	37%	30%	32%	25%	29%

tion of Grade III tumors than the colon and over twice as high a proportion of advanced cases with metastatic nodes, but the difference is less than might be expected. Rankin and Olson had 58, 48, and 51 per cent five-year survivors without evidence of disease in the right colon, left colon, and combined group, respectively. Their results show a high incidence of survival but the operative deaths, cases lost to follow-up and dead from other causes were not included.

TABLE XIX

FOLLOW-UP RESULTS

Operative Deaths, Cases Lost to Follow-Up and Cases Dead from Other Causes Not Included

	Right Colon	*Left Colon*	*Right and Left Colon*	*Rectum*	*Colon and Rectum*
Cases dead of disease or alive five years with or without disease	14	48	62	64	126
Five-year survivors:					
Cases	10	26	36	32	68
Per cent	71%	54%	58%	50%	54%
Five-year survivors without evidence of disease:					
Cases	10	24	34	27	61
Per cent	71%	50%	55%	42%	48%

A comparison of the results with and without node metastases showed, as might be expected, a much better prognosis when the nodes were not involved. Of the combined colon and rectal cases without node metastases, 34 per cent survived five years and were free of disease as compared to 16 per cent of the cases with lymph node metastastes. The results were slightly better in the colon than in the rectum when the nodes were not involved, and about the same when they were. The best results were seen in the right colon when the nodes were negative and the poorest when positive. The cases without node metastases represented 73 per cent of all the cases, and those with metastases 27 per cent. This ratio is probably not accurate and should show a higher figure for the cases with involved nodes because of inadequate examination of the lymph nodes in the earlier cases in the series.

Of the 27 "colloid" tumors, seven, or 26 per cent, were alive over five years without disease. This figure is based on all the "colloid" cases and includes operative deaths, cases lost to follow-up, and those dying from other causes. Only one case with involved nodes survived five years. The 17 "colloid" tumors that were not of the signet-ring type showed four, or 24 per cent, living five years without evidence of disease. This result is slightly poorer than the 29 per cent average for the whole series. As most of these "colloid" tumors fell into Grade I, histologically, one would have expected a better result. Of course, the group is entirely too small to warrant a definite conclusion. All cases with involved nodes died with recurrences within five years. Only eight of the 17 cases had follow-ups that permitted analysis.

There were 10 signet-ring tumors in all. Seven had follow-up records suitable for study. There were three five-year survivors without disease, or 30 per cent. Here again the number is too small for any definite conclusions.

Although the five-year results in the two types of colloid tumors have been similar, the higher proportion of Grade III tumors and the much higher incidence of node metastases in the signet-ring cases suggest that they are a particularly malignant group. Parham,[17] Raiford,[9] Rankin and Broders,[2] Ochsenhirt,[15] and Rankin and Chumley[16] hold the same view.

SUMMARY

(1) A series of 223 cases of carcinoma of the colon and rectum has been studied. Adequate follow-up records were obtained in 205, or 92 per cent.

(2) The following four criteria for histologic grading were found to be of value from our follow-up results: Glandular arrangement, invasiveness, nuclear polarity, and number of mitoses.

(3) Both a numerical and nonnumerical method of grading were tried, based on the four criteria selected. As both gave very similar results, the nonnumerical method was adopted because of greater simplicity. Three grades of malignancy were used instead of the usual four.

(4) Most of the cases were Grades I and II. The percentage of Grade I tumors was 19 per cent higher and that of Grade III tumors 16 per cent lower in the colon than in the rectum, suggesting that colon tumors tend to be better differentiated. Simple "colloid" tumors were mostly Grade I, and those of the signet-ring type nearly all Grade III.

(5) A definite relationship was found between the follow-up results and the grades. The chances of living five years without recurrences were three times as good for the Grade I cases as for the Grade III cases. The same relationship was seen when the cases with and without node metastases were studied separately, although it was less striking. The incidence of metastatic lymph nodes increased with the grade.

(6) The distribution of cases according to Dukes' classification showed a higher proportion of advanced C cases in the rectum than in the colon, with a correspondingly smaller proportion of A cases. Only two out of 69 cases showed node metastases before the bowel wall had been penetrated. Dukes' generalization in this regard has been shown by our series to apply to the colon as well as the rectum.

(7) Follow-up results according to Dukes' classification showed striking differences between the A, B, and C cases. No definitely proven A case died after operation from recurrence. The chance of five-year survival without disease was over four times as good for the A as for the C cases. The value of this classification in prognosis is obvious.

(8) A definite relationship was found between the grades and Dukes' method of classification. Most of the A cases were found, histologically, to be Grade I, and very few Grade III, whereas C cases were mostly Grade III

and very rarely Grade I. The extent of spread of a tumor at operation is of the greatest importance in prognosis in any particular case, but is in turn based primarily on the rate of growth as evidenced by the grade of the tumor. Both criteria should be used in prognosis to supplement one another. A classification combining both the grade and Dukes' method is presented.

(9) Lymph node metastases occurred in 27 per cent of cases in the whole group and were twice as frequent in the rectum as in the colon. They were present in 30 per cent of the "colloid" cases, occurring in 50 per cent of those of the signet-ring type and in 18 per cent of the other "colloid" cases. The incidence of five-year survival was two and one-half times higher when the nodes were not involved than when they were.

(10) Tumors classed by gross examination as projecting gave far better five-year results than those classed as infiltrating. Most of the projecting tumors were, histologically, Grade I, and the infiltrating Grade III.

(11) Variations in histologic grade in different parts of the same tumor were frequent. The grade of the tumor in the metastastic nodes was usually the same as that found in the main tumor. In 78 per cent of the 76 rectal tumors in which biopsies were taken, the biopsy showed the same grade as the tumor. In 22 per cent of cases, the biopsy was at least one grade less malignant. In no case was it more malignant.

(12) The presence of enlarged lymph nodes is not a reliable indication of metastases. In 97 cases in which the nodes were reported enlarged, only 38 per cent contained metastases.

(13) No relationship could be found between the age of the patients and the five-year results.

(14) The follow-up results which included operative deaths, cases lost to follow-up, and dead from other causes, showed 29 per cent living five years without disease for the combined group, 32 per cent for the colon, and 25 per cent for the rectum.

(15) Of the 17 "colloid" cases not including the signet-ring type, 24 per cent survived five years without evidence of disease, as compared to 30 per cent of the 10 signet-ring cases. Both series, however, are too small to warrant conclusions.

(16) The five-year results without evidence of disease in cases both with and without node metastases showed 34 per cent for the former, and 16 per cent for the latter in the combined colon and rectum group. If the nodes show metastases, the prognosis for five-year survival both in the colon and rectum is just about one-half as good.

CONCLUSIONS

The grading of colon and rectal tumors is of definite value for prognosis. It is of less value, however, than the classification of these tumors according to their extent of spread, as outlined by Dukes. A combination of these two methods may prove even more effective.

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MALIGNANT TUMORS OF THE SALIVARY GLANDS *

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IN THE earlier reports on tumors of the salivary glands appearing at the end of the eighteenth and the beginning of the nineteenth centuries, no clear distinction was made between those arising in and derived from the salivary glands and other tumors appearing in the regions of the salivary glands but not actually of salivary gland origin. It is probable that certain inflammatory and granulomatous lesions were included. The first attempt at classification seems to have been made by Bérard[1] in his thesis published in 1841. Additional knowledge concerning the character of salivary gland tumors was gained through the works of Lebert,[2] Broca,[3] Richard,[4] and Dolbeau[5] (1850–1858). Their true origin became recognized, and they were described as adenomata or enchondromata. Billroth[6] (1859) and Virchow[7] (1863) made rather detailed gross and microscopic studies and noted their complex structure. Von Bruns[8] (1859) made an histopathologic study of the material from a considerable number of cases and was regarded by Volkmann[9] (1895) as the founder of our knowledge on the subject. Apparently the name "mixed tumors" was established through an article published by Minssen,[10] in 1874, in which they were referred to as "*gemischte Geschwülste.*"

During the latter half of the nineteenth century, the origin of salivary gland tumors was a matter of lively interest and difference of opinion. There were three principal schools of thought. One school believed they were derived from connective tissue and, therefore, mesenchymal in origin; Billroth,[6] Virchow[7] and Kaufmann[11] were the chief protagonists of this theory. A second group believed that vascular endothelium constituted the tissue of origin; the names of Kolaczek,[12] Wartmann,[13] Nasse[14] and Volkmann[9] are prominently associated with this group. Volkmann, more than any other, was responsible for the popularization of the endothelial hypothesis. A third group believed that the complex nature of salivary gland tumors could best be explained upon the assumption of branchial origin; Cohnheim,[15] Birch-Hirschfeld,[16] Cunéo and Veau,[17] and Fredet and Chevassu[18] are closely identified with the earlier development of this thought. A fourth group, largely influenced by the work of Hinsberg,[19] believed that detached or displaced embryonal salivary gland cells were responsible for the later formation of tumors. A fifth group, largely of the French school, attributed the development of salivary gland tumors to a simple direct origin from glandular

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epithelium; Verneuil,[20] Planteau[21] and Duplay[22] were supporters of this point of view.

It cannot be said that any wholly satisfactory hypothesis has been developed. Difficulty has been encountered in offering a suitable explanation for the frequent occurrence together of epithelial, cartilaginous, myxomatous and fibrous tissues in a single tumor. The majority of investigators subscribe to the theory of epithelial origin, but there is some difference of opinion as to the actual mode of development. Pitancé,[23] in 1897, suggested that the parenchymal cells of mixed tumors were derived from masses of cells left in or about the gland during the process of development. Hinsberg[19] did a large amount of embryologic research, the results of which supported the epithelial origin of salivary gland tumors and indicated that they arise from embryonal glandular elements. Wilms[24] and Wood,[25] however, have placed the time of detachment of epithelial cells to a still earlier period of embryonic development. According to their belief the detachment occurs before the salivary glands are formed. It is not, therefore, embryonic parotid tissue which becomes disorganized but rather a displacement of the buccal epiblast from which the parotid is subsequently to be formed. Some underlying mesoblast is assumed to be included in the ectopic process. By the assumption of an early displacement it is easier to explain the presence of epithelial cells with intercellular bridges or spines which have frequently been observed in salivary gland tumors. The close association of cartilage, myxomatous tissue and other structures of mesoblastic origin also becomes more comprehensible.

To further clarify the probable manner of growth of salivary gland tumors, it appears worth while to review in some detail the embryonic development of a normal gland. According to Hammar[26] the beginning of parotid development is seen by the end of the first month, the embryo then being about 8 Mm. long. A groove appears in the sulcus of the cheek near the angle of the mouth. Grosser[27] and his associates describe the further development as follows: "At first quite small, the furrow gradually elongates, and before the embryo has reached a length of 17 Mm. it separates from the epithelium and forms a tubular structure lying beneath the epithelium of the alveolobuccal groove and opening into the mouth cavity at a point which corresponds with the anterior end of the original furrow. Mesenchymatous tissue gradually forces its way between the tube and the alveolobuccal epithelium, and the tube, increasing in length, pushes its way back over the masseter muscle to the neighborhood of the external ear. As it comes into this region the tube or duct, as it may be called, begins to branch at its posterior extremity, the branches being at first solid outgrowths from the wall of the duct, and, as these increase in number and size and become surrounded by a mesenchymatous capsule, the gland assumes the position and general form of the adult structure. . . . The histogenetic development of the salivary glands is not completed until some time after birth, probably not until after the child is weaned. The canalization of the solid anlagen of the glands proceeds peripherally, and so long as the terminal branches remain solid they have

the power of producing additional buds. When, however, the lumen is formed in a bud and it becomes an alveolus, its power of budding is lost, and the further increase in the size of the gland is due to the development of the investing connective tissue and to an increase in the size of the alveoli already present."

Our special attention is drawn to the apparent capacity of the solid anlagen of glands to continue to grow and produce buds until canalization takes place. If groups of cells became detached from the embryonic gland or from buccal epiblast and were subsequently activated, it is quite conceivable that their development might follow a course of the fetal type. Faulty canalization or failure of canalization would be followed by continued epithelial budding and growth. With the concomitant development of an investing connective tissue capsule, a tumor would be formed. If growth were orderly and development of the capsule kept pace with the epithelial elements, such a tumor should remain encapsulated and benign. If, on the contrary, the rate of epithelial proliferation became excessive, there would be invasion of adjacent tissues, and the tumor would be called malignant.

Salivary gland tumors, if derived from primitive embryonal tissues, may reasonably be expected to show considerable diversity of structure and this indeed is the case. A number of types are found in both the benign and malignant groups. The common types of malignant tumors are: (1) The mixed tumors with malignant changes; (2) tumors composed of small cells of the basal type either with solid or cylindromatous arrangement; (3) papillary cystic tumors; (4) adenocarcinomata; (5) squamous cell carcinomata; and (6) a somewhat heterogeneous group, usually rather undifferentiated, and not conforming to any of the preceding classifications.

The tumors behave, clinically, somewhat as their cellular structures would indicate. Metastatic lesions generally follow the pattern of the original tumor. In the case of the malignant mixed tumors the secondary implants usually appear in simpler form. Occasionally, however, the metastatic tumors greatly resemble ordinary mixed tumors, even to the extent of being circumscribed or encapsulated. Such cases have been reported by Tommasi,[28] Griffini and Trombetta,[29] Barozzi and Lesné,[30] Le Dentu,[31] Partsch,[32] Kornblith[33] and McFarland.[34]

When metastasis occurs, the regional lymph nodes are occasionally involved but not with great frequency. In 27 cases from the records of St. Luke's and New York Hospitals (Tables I and II) lymph node involvement was proved in only four, approximately 15 per cent. Metastasis to the lungs was demonstrated roentgenologically in eight of the 11 cases which were examined, an incidence of approximately 30 per cent for the entire series. In 16 patients no roentgenologic examinations of the chest were made. It is quite possible that a more complete study of this group would have added to the incidence of pulmonary metastasis. Bones were involved in two cases. General metastasis occurred in one case. In 82 cases of definite malignancy of the large salivary glands, reported from the Radiumhemmet by

Ahlbom,[35] metastases were reported in the lymph nodes in nine instances (11 per cent), seven to lungs (8.5 per cent), seven to bones, and five cases with general metastasis. In 42 cases, reported by Stein and Geschickter,[36] there was enlargement of the cervical lymph nodes in 13, or 30.9 per cent. Actual metastasis, however, was proved in only one case. Metastasis to the lungs apparently was not observed in any case. Mediastinal metastasis was recorded in one case. The authors state that distant metastases are extremely rare.

The development of metastatic lesions does not appear to bear a close relationship to the duration of the disease. One patient (Table I, No. 121–135) had histologically proven metastasis to a cervical node and roentgenologic evidence of pulmonary metastasis, both in less than two years after the apparent onset of the primary tumor. Another patient (Table I, No. 293–784) showed no roentgenologic evidence of pulmonary involvement nine years after onset, but the following year unmistakable shadows were present. Additional examples of delayed metastasis are to be seen in Figures 1 and 2.

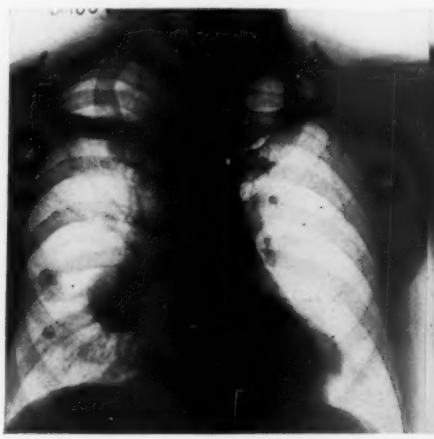

FIG. 1.—Case 59045, Table I: Roentgenogram of chest, 21 years after appearance of original parotid tumor, showing pulmonary metastases. It is probable that the tumor was primarily benign and that malignancy was a later development. The patient lived two years and four months after this roentgenogram was taken and had very few subjective symptoms.

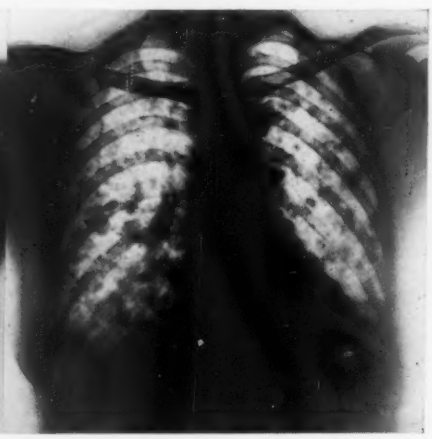

FIG. 2.—Case 95866, Table I: Roentgenogram taken 20 years after appearance of a submaxillary tumor showing extensive pulmonary involvement. The primary tumor had been excised 19 years before and histologically diagnosed as a "mixed tumor."

The tendency of malignant salivary gland tumors toward remote metastasis, with relatively infrequent involvement of the regional lymph nodes, is in marked contrast with the behavior of other malignant epithelial tumors arising in the same general vicinity. Carcinoma of the tongue and buccal mucosa, for example, regularly metastasizes to the cervical lymph nodes and rarely extends beyond them. Billroth[6] was impressed by the relative infrequence of regional lymph node involvement in carcinoma of the salivary glands, and concluded that these tumors rarely gave rise to metastasis.

Tumors of the salivary glands, as recorded from a number of clinics, have shown considerable difference in the incidence of malignancy. Wood[25] placed

it at 25 per cent of the face and neck group. Nasse[37] found two carcinomata and two sarcomata in 36 cases, 11 per cent. Volkmann[9] reported one carcinoma and one fibrosarcoma in 33 cases, 6 per cent. In the group of cases from the Massachusetts General Hospital, Benedict and Meigs[38] recorded 41 benign tumors, 21 carcinomata, and nine sarcomata, an incidence of malignancy amounting to 42 per cent. In the series of parotid tumors reported by Stein and Geschickter,[36] there were 42 malignant tumors in a total of 241 cases, 17.4 per cent. Ahlbom[35] reported 82 cases of definite malignancy in 193

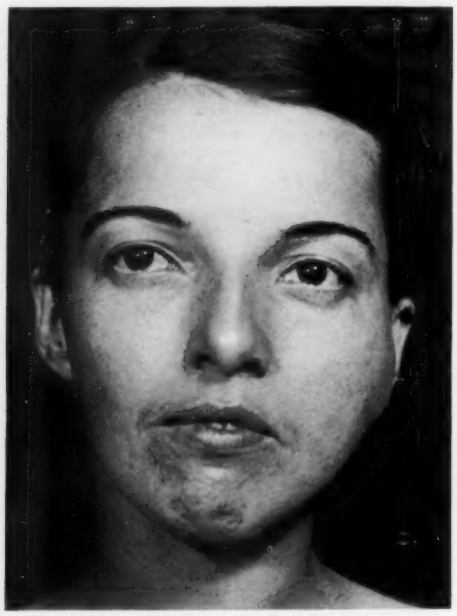

FIG. 3.—Carcinoma of the parotid occurring at the age of 29. The rather smooth contour and gentle slope of the tumor indicate its infiltrating character. Benign lesions are frequently irregular and often stand out in a more striking manner.

tumors of the large salivary glands, 42 per cent. In 150 consecutive cases from the records of St. Luke's Hospital, New York, Shore[39] found malignant tumors making up 11 per cent of the total. Among the entire population, however, malignancy is relatively infrequent. The 82 cases reported by Ahlbom constitute the largest series thus far assembled.

The symptoms are few and by no means pathognomonic. A small nodule or swelling appears without apparent cause and increases in size, usually slowly, but sometimes rapidly. There may be a history of the previous removal of a tumor from the same gland. When a tumor recurs after being removed completely and without rupture of its capsule, malignancy should be suspected even if the original tumor was histologically benign. As a rule there is no pain; when present, it is usually described as shooting or stabbing in character and is referred to the jaw, side of head, or ear. A large growth sometimes interferes with motion of the jaw; attempts to open the mouth

widely may cause pain by compressing the tumor. In advanced cases there is frequently a spontaneous facial paralysis due to nerve involvement.

In appearance, the malignant tumor cannot be accurately distinguished from one which is benign. Frequently the malignant lesion appears as a rather even elevation with margins which are not well defined (Fig. 3), whereas, the benign tumor often presents as a precipitous, nodular swelling. On palpation the malignant tumor is usually quite hard and fixed to the deeper structures. Less frequently there is fixation to the skin as well. In late cases there may be ulceration or a facial paralysis. The limits of the tumor as a rule are not easily defined. The palpation of more than one tumor mass is strongly suggestive of malignancy. A benign tumor is ordinarily a well encapsulated, freely movable, firm, resilient, often lobulated, single tumor.

Other conditions which may be confused with tumors of the salivary glands are those affecting the groups of lymph nodes which are intimately associated with glands. Branchiogenic tumors and cysts, tumors of the jaws, and inflammatory conditions are also mistaken, now and then, for new growths of salivary gland origin.

Histologic differentiation of benign and malignant salivary gland tumors is sometimes extremely difficult. A malignant tumor may appear encapsulated and be indistinguishable microscopically from a benign growth. The diagnosis in such cases depends ultimately upon the clinical course of the disease. In the average case the histologic diagnosis is made with relative certainty.

Treatment of the malignant tumors is far from satisfactory. Radical surgery frequently carries the handicap of producing facial nerve paralysis when applied to parotid tumors, and these constitute the great majority. In many cases it also fails to completely eradicate the tumor. Radiation has the disadvantage of threatening the integrity of normal tissues, especially the skin, if given in dosage sufficient to destroy the tumor. A combination of surgery and radiation appears to have given better results than either used alone and has been adopted as the standard treatment in a number of clinics. There is, however, considerable variance in the experiences and views expressed in the literature. Wakeley,[40] Benedict and Meigs,[38] and McFarland[34] saw little benefit from radiation, whereas, Quick and Johnson[41] apparently regarded it as the treatment of choice. Bérard,[42] Wickham,[43] Caussé,[44] Hintze,[45] Ahlbom[35] and, in fact, most clinicians of to-day favor a combination of the two agencies.

The application of both surgery and radiation in the treatment of a particular case naturally raises the question as to which is chiefly responsible for the result obtained. A conclusive answer to this question has not been reached and must await further experience. The quality of surgery or radiation employed and the type of tumor are, no doubt, matters of importance. Surgery which does not completely remove the tumor cannot be expected to effect a cure; the same is true of radiation which fails to destroy

all of the tumor cells. To a restricted degree, each method can supplement the work of the other, but it is also true that there is an overlapping of their limitations, particularly in the case of advanced lesions.

The complications associated with surgical extirpation are those incident to any other operation of like magnitude about the face and neck. There are, in addition, the injuries to the facial nerve which are frequently made necessary by inclusion of the nerve in the tumor mass. When a complete division has been produced, it is sometimes possible to restore continuity by suture of the nerve ends. If the ends are separated by a considerable distance, the nerve grafting procedure described by Duel[46] may be tried. Another procedure is the grafting of the spinal accessory[47] or the hypoglossal[48] nerve to the distal segment of the facial. If it is impossible to restore innervation, fascial transplants[49] or muscular rearrangements[50] may be made in order to ameliorate the condition.

The principal complications of radiotherapy are the occasional radiation necrosis, atrophic changes in the skin and deeper tissues with postradiation dermatitis or ulcer, and atrophy of the salivary and mucous glands with consequent dryness of the mouth. Heavy radiation is also sometimes followed by facial paralysis.

Prognosis in the individual case is a matter of great uncertainty. If untreated, the disease progresses at a rate which cannot be predicted. In some cases it runs a very slow course over many years, in others the progression is rapid and death may occur within a year of the apparent onset. Death may come through gradual exhaustion, from ulceration with infection or hemorrhage, from pulmonary or other metastasis, or from intercurrent disease.

In the treated cases a certain rather low salvage is obtained. Surgery alone gave 20 per cent of three-year remissions and 13 per cent of five-year remissions in the 42 cases reported by Stein and Geschickter.[36] Hintze[45] reported a five-year remission in 26 per cent of a series treated mainly by surgery with some postoperative radiation. Benedict and Meigs[38] could report out of 30 malignant tumors of the parotid only one living and well three years after treatment. All were treated by surgery, with or without radium.

In 62 cases of malignant salivary and mucous gland tumors treated by radiation alone, Ahlbom[35] reported that 39 had been followed for five years and that nine, or 23 per cent, were free of signs and symptoms. Of 55 cases followed three years, 15, or 27 per cent, were well.

Ahlbom reported, in the same article, 62 similar cases treated by surgery and radiation combined. Thirty-five had been followed five years and 14, or 40 per cent, were free of disease. Fifty-five had been followed three years, and 27 of these, or 49 per cent, were well. In 82 cases of definitely malignant tumors of the large salivary glands analyzed in Ahlbom's series, there were 12, or 14.3 per cent, who survived five years or more without recurrence. There were six others, 7 per cent, free of recurrence for more than three but less than five years. One of the five-year survivors was treated by radiation alone; all the others had surgery and radiation. Bérard[51] and his asso-

ciates have reported 15 cases of histologically verified cancer of the parotid treated by a combination of surgery and radiation with five, or 33 per cent, well after three years and three, or 20 per cent, well after five years.

In 27 cases of carcinoma of the large salivary glands taken from the records of St. Luke's and New York Hospitals (Table I), all except two had one or more attempts at surgical extirpation. None had preoperative radiation. Fourteen had postoperative radiation. Two were treated by roentgenotherapy alone, after a preliminary biopsy.

Out of the group of 27 patients, only three, approximately 11 per cent, are known to have been living and well more than five years after operation. One of these, with a parotid carcinoma, had a single operation with no radiation and is now well ten years after operation. Another patient with parotid carcinoma had two operations with postoperative radiation and is known to have been well seven years after the second operation. A patient with a submaxillary salivary gland carcinoma had a single operation with no radiation and is now living and well nine years after operation. One patient, Dr. M. K. Smith's case, with a sublingual salivary gland carcinoma, is living 17 years since the appearance of the tumor and nine years since the last operation, but has local recurrence and metastasis to the lungs. Operation in this case was followed by roentgenotherapy.

In addition to the survivals of more than five years, there are some of shorter duration. One patient, who had a parotid carcinoma, is well two years and seven months after operation, and another who had submaxillary carcinoma is well two years and six months after operation. There are seven additional patients who are apparently free of disease, but all for a period of less than two years. It is possible that the continued survival of some of this group will increase the number of five-year remissions.

As a rule, carcinomata of the large salivary glands are visible, palpable, accessible tumors, characterized by slow growth and late metastasis. According to the usual criteria, such tumors should lend themselves readily to treatment and offer a good prognosis. It is obvious, however, that such has not been the case. The intimate association of parotid tumors with the facial nerve unquestionably accounts for many failures, particularly in surgical treatment. Patients are frequently advised to ignore tumors in the parotid gland because there is danger of injury to the nerve. Facial paralysis is a serious handicap and neither patient nor physician can be blamed for wishing to avoid it. It is to be remembered, however, that from 10 to 40 per cent of the large salivary gland tumors are either primarily malignant or become malignant. If such a tumor is permitted to grow, the time inevitably comes when it must be removed under conditions which make nerve destruction almost a certainty. It is undoubtedly better to advise removal of all salivary gland tumors when they first come under observation. In the case of a benign tumor serious damage to the facial nerve is seldom necessary. If the tumor is malignant, early removal offers the best chance of avoiding nerve injury and of cure.

TABLE I

MALIGNANT TUMORS OF THE SALIVARY GLANDS

Records of St. Luke's and New York Hospitals

History No.	Sex	Age	Duration of Tumor Before First Treatment	Treatment: Number of Operations	Treatment: Radiation: Preoperative	Treatment: Radiation: Postoperative	Histologic Diagnosis	Metastasis: Cervical Nodes	Metastasis: Lungs	Metastasis: Bones	Metastasis: General	Living: Since Appearance of Tumor	Living: Since Last Operation	Died of Recurrence: After First Appearance of Tumor	Died of Recurrence: After Beginning of Treatment
PAROTID GLAND															
124–926	M.	54	4 yrs.	1	—	—	Carcinoma	—	—	—	—	4 yrs. 6 mos.	6 mos.	—	—
121–684	F.	67	1 yr.	1	o	o	Squamous cell carcinoma	—	—	—	—	2 yrs.	1 yr.	—	—
121–135	M.	54	8 mos.	2	o	o	Carcinoma	+	+	—	—	1 yr. 9 mos.	6 mos.	—	—
104–777	F.	29	8 mos.	3	o	o	(1) Pap. cystad. (2) Adenocarcinoma	—	—	—	—	4 yrs. 7 mos.†	2 yrs. 7 mos.	—	—
91993	F.	52	1 yr.	16	—	+	Carcinoma	—	+	+	+	—	—	11 yrs.	10 yrs.
88910	M.	45	1 yr.	6	—	+	Adenocarcinoma	—	—	—	—	—	—	6½ yrs.	5½ yrs.
85895	F.	56	6 mos.	1	—	+	Carcinoma, pap. type	—	+	+	—	—	—	2 yrs.	1½ yrs.
75813	M.	40	9 mos.	1	o	+	Squamous carcinoma	—	—	—	—	—	—	12 mos.	3 mos.
75735	F.	40	—	1 (biopsy)	—	+	Squamous carcinoma	—	—	—	—	—	—	—	—
66353	M.	36	5 yrs.	3	—	—	Carcinoma	—	—	—	—	—	—	—	—
66061	F.	47	2 yrs.	1	—	—	Epithelioma	—	—	—	—	12 yrs.	10 yrs.	—	—
59045	M.	55	17 yrs.	7	o	+	(1) Mixed tumor (2) Carcinoma	o	+	o	o	—	—	22 yrs.	5 yrs.
1241	M.	65	—	1	—	—	Carcinoma	—	—	—	—	—	—	—	—
47	M.	34	—	5	—	+	Carcinoma	+	—	—	—	—	—	—	13 yrs.
195–872	M.	53	2 yrs.	2	o	+	Squamous and adenocarcinoma	+	o	o	—	6 yrs.	2 mos.	—	—
293–784	F.	20	2 yrs.	4	o	+	(1) Adenocarcinoma (2) Mixed tumor	—	+	o	o	10 yrs.	4 mos.*	—	—
101–732	M.	34	—	3	o	+	Malignant mixed tumor	—	—	—	—	—	1 yr. 7 mos.	—	—
295754	F.	37	3 yrs.	1 (biopsy)	—	+	Carcinoma	—	+	—	—	—	—	4 yrs.	1 yr.
294149	F.	16	3 yrs.	2	—	+	Adenocarcinoma	—	—	—	—	—	7 yrs.	—	—
295944	M.	58	7 mos.	1	o	—	Carcinoma	+	—	—	—	—	—	—	—
236160	F.	40	8 yrs.	1	—	+	Basal cell carcinoma	—	—	—	—	—	—	11 yrs.	3 yrs.
288965	M.	40	2½ yrs.	1	—	—	Adenocarcinoma	—	—	—	—	—	4½ mos.	—	—
SUBMAXILLARY GLAND															
95866	F.	44	6 mos.	4	o	+	(1) Mixed tumor (2) Carcinoma, cylindroma type (3) Mixed tumor	—	+	—	—	—	—	20 yrs. 6 mos.	20 yrs.
73381	M.	57	6 mos.	1	o	o	Carcinoma	—	—	—	—	9 yrs. 6 mos.	9 yrs.	—	—
138–278	F.	68	2 yrs.	1	o	+	Carcinoma	—	o	—	—	3 yrs. 5 mos.	1 yr. 5 mos.	—	—
118–401	M.	67	3 mos.	1	o	—	Epidermoid carcinoma	—	o	—	—	—	—	9 mos.	6 mos.
SUBLINGUAL GLAND															
94198	F.	31	3 yrs.	8	o	+	(1) Mixed tumor (2) Adenocarcinoma	—	+	—	—	17 yrs.†	9 yrs.	—	—

* Living; with metastases.

† Living; with recurrence and metastases.

SUMMARY

Malignant tumors of the salivary glands in the great majority of cases are epithelial in origin and are classified as carcinomata.

They probably arise in displaced embryonal cells of the salivary glands or more likely from the buccal epiblast with some underlying mesoblast.

They exhibit a wide variety of histologic structure and of clinical behavior.

They affect the sexes in nearly equal numbers and may occur at almost any age. The youngest of the present series was 16 years old, the oldest 68 years; the majority appeared in middle life.

Some apparently arise as malignant tumors while others appear to be the result of malignant changes in primarily benign tumors.

The disease may run a fatal course within a few months or the patient may survive for many years with the disease.

Metastasis to the regional lymph nodes is relatively infrequent. The incidence was approximately 15 per cent in the present series of 27 cases.

Metastasis to the lungs is perhaps more common than is generally recognized. Eleven patients of this series had roentgenologic examinations of the chest. Eight showed convincing evidence of pulmonary metastasis, an incidence of 72 per cent of those examined and approximately 30 per cent of the entire series. A roentgenogram of the chest should be a routine procedure in the study of these cases.

The treatment which appears to have given the best results is surgical extirpation combined with radiotherapy.

The result in a given case cannot be predicted with any great accuracy. The general prognosis can scarcely anticipate the ultimate cure, or five-year survival, of more than 25 per cent.

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94198 F. 31 3 yrs. 8 0 + — + — — — 17 yrs.† 9 yrs. —

(1) Mixed tumor
(2) Adenocarcinoma

* Living; with metastases. † Living; with recurrence and metastases.

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DISCUSSION.—DR. N. CHANDLER FOOT (NEW YORK): The origin of tumors of the salivary glands is still far from being settled. A good many authorities are inclined to the fetal rest theories, rather than that of parotid origin. The theory of their origin from portions of the buccal epiblast is particularly alluring. Their origin from the parotid itself would scarcely explain the very pleomorphic structure of these tumors. On the other hand, unmixed tumors do occur in the parotid and these are quite uniform structures. This may mean that some of the group do indeed arise from salivary gland, but it might also indicate that only one element of the buccal epiblast has expressed itself in the tumor. It may be, too, that there are more than one source of origin for these tumors. This, however, would seem to be rather far-fetched.

Doctor MacFee has spoken of tumor growth outstripping capsular growth and thus breaking out into the surrounding tissue to become malignant. This breaking through the capsule is a good starting point for formulating tumor malignancy in these cases as, unfortunately, one can tell very little histologically. To many tumors that Doctor Foot has seen, he would unhesitatingly have given a clean bill of health, had he known nothing of the surgical history of the case. On the other hand, outspokenly malignant-looking examples may be well encapsulated and often bring contumely upon the pathologist who views them with alarm and gives a gloomy prognosis. Doctor Foot had had a patient with a completely innocent-looking tumor return on three occasions to the hospital, the last time with apparent pulmonary metastases. This tumor was very poorly, if at all, encapsulated, and invaded the muscle in the parotid region. For these reasons, Doctor Foot felt it of the utmost importance that the pathologist should be acquainted with the surgical data concerning a mixed tumor of the parotid, before attempting to give a prognosis.

The large tumor of unmixed nature, that Doctor MacFee removed from the parotid region, was grossly opaque, light yellow and very firm, so that it resembled parotid tissue somewhat. Under the microscope, however, it seemed to be made up of cords of cuboidal cells with a delicate stroma filled with capillaries, separating the cords and resembling the structure of a paraganglioma and hence carotid body. Doctor Foot could not quite make up his mind whether this was a carotid body tumor displaced slightly higher than usual, or a rather atypical offspring of the parotid which had failed to take on mixed characteristics.

DR. ROBERT H. KENNEDY (NEW YORK) called attention to one very black side of the tumors under discussion worth emphasizing, at least as they present themselves at the Skin and Cancer Hospital. Almost invariably, when operation is performed upon them there, it is anywhere from the second to to the tenth or twelfth time. The impression is gained there that most of these tumors originally were operated upon by a surgeon or a general practitioner who took them as a rather simple procedure, operating most commonly under local anesthesia, believing that the tumor, which is apparently possibly 1 cm. or 1.5 cm. in diameter, represents the entire growth, when as a matter

of fact it really represents the prominence of the parotid fascia over a tumor that has not yet broken through, or if it has broken through, the fascia does not disclose the deep part at all. In view of the statistics presented by Doctor MacFee regarding chance of recovery, and the fact that the pathologist cannot tell in many cases which are the malignant tumors and which are not, the small tumors that one sees in the parotid region deserve particular preparation for very thorough operation the first time one sees them. Doctor Kennedy said he felt that the procedure he had learned from Doctor Semken was the best one to carry out for these tumors, namely, a crucial incision for a parotid tumor of any size at all, then dissecting up the four quadrants and suturing them back. The dissection is made as much as possible from above downward so that one runs in the direction of the facial nerve. If there is any possibility that that nerve runs through the tumor, it is, of course, most essential to attempt to save it. Occasionally one finds that the tumor is in the superficial portion of the parotid and has so compressed the major portion of the gland that the facial nerve is well pressed away from the tumor, still lying in the parotid tissue.

Doctor Kennedy felt that it was inexcusable to use radiotherapy in preference to operation, as is still practiced in a good many cases. He had never seen it do anything except possibly cause recession for a time, and in numerous cases where a biopsy was performed with a diagnosis of benign tumor, after multiple radiation treatments, the patient comes in with a very malignant growth.

Dr. Hugh Auchincloss (New York) said that of recent years the seriousness of the prognosis in these cases had come to be more fully appreciated. It seems plausible, owing to the frequency of lung metastases in these cases, to perform a preliminary ligation of the external and internal jugular veins, if an attempt at removal be made. It is more than likely that these tumors have their distribution by means of the blood stream.

Doctor Auchincloss described a patient, a middle aged woman, who was sent to him within the last year in consultation from a neighboring state. A small specimen had been removed from the right parotid region previously. The left parotid was swollen and strongly suggested new growth. He removed a specimen from the left side and Doctor Stout made the diagnosis of a reticulocytoma. A Wassermann reaction was not done at that time, but shortly afterwards it was done and found to be double 4 plus. It is probable that she had congenital syphilis. In spite of this, Doctor Stout thinks that the Wassermann reaction had nothing to do with it, and it is more than likely that he was right. In all events, both sides have been treated by roentgenotherapy, with a resultant very rapid subsidence. One cannot be at all sure, however, that this has cured her. It is not unlikely that it may appear elsewhere. She has also been given antisyphilitic treatment.

Another small tumor, that Doctor Auchincloss stated he had seen, was in a woman of middle age. It was removed and found to be a so-called "mixed, or composite tumor." Within two years it recurred. It was again removed, and treatment by radium inaugurated, which resulted in a very definite subsidence of the growth. Two years later, she was submitted to very heavy radiation at Johns Hopkins Hospital because of the diffuse persistence of the disease, with facial paralysis. Three weeks ago she died.

As brought out so ably by Doctor MacFee, these tumors should be regarded with great concern. Doctor Auchincloss said he had records of a few other cases that have remained well, in younger people.

DR. JOHN M. HANFORD (NEW YORK) said that the record of Dr. A. P. Stout, estimated for a ten-year period (1915–1924), at the Presbyterian Hospital, indicates that in that period there were only three carcinomata of the parotid gland—of all the salivary glands in fact—in a total of 1,862 cases of carcinoma. It is a rare condition. He asked Doctor MacFee what his procedure is when he operates upon a supposed composite tumor (Doctor Hanford felt sure that carcinomata are not usually diagnosed beforehand, especially the small ones) and concludes, or suspects, during the operation that it is carcinoma.

Doctor Hanford disagreed somewhat with both Doctor Foot and Doctor MacFee in their discussion of the encapsulation of composite tumors. His impression was that they really do not have capsules—that is, neither the carcinoma nor even the mixed or composite tumor. They are circumscribed and appear to have capsules in the sense that a fibroma has a capsule, but he believed that even the composite tumor has not a real capsule. He would also disagree with Doctor MacFee, though having learned a great deal from him, that the most common thought one should have, when a composite tumor has been operated upon and recurrence appears, is that the reappearance is indicative of malignancy. The reappearance of these tumors after attempted excision is very common. The fact is that occasionally even after enucleation of what appears to be a capsule, there are still some composite tumor cells left in the parotid gland.

DR. MORRIS K. SMITH (NEW YORK) said that in his case—tumor of the sublingual gland—the tumor palpated in the floor of the mouth was about the size of a peanut, and it was excised through an incision in the floor of the mouth. The first recurrence was treated similarly. He said, however, that although he probably would not have the chance to operate upon another sublingual mixed tumor, he would—if he did have such an opportunity and were sure of the diagnosis—make an approach, even though it involved undertaking a considerably more extensive procedure, which insured a wide removal without any risk, if possible, of leaving behind a portion of it. In operating in as small a field as the floor of the mouth it is technically extremely easy not to accomplish a complete enucleation, particularly if the capsule is very thin and there are cysts.

DR. HERBERT WILLY MEYER (NEW YORK) emphasized that cancer of the parotid gland is of vital import to the patient as well as to the surgeon, if a radical operation is indicated with the resulting injury to the facial nerve, particularly in the female.

From a survey of the records of the past ten years at the Lenox Hill Hospital, made by Dr. Richard Kessler, Doctor Meyer noted nine cases of malignancy of the parotid salivary gland. The youngest case was in a child, age 4, who had a sarcoma of the parotid, proven by biopsy, which was treated by deep roentgenotherapy, held partially in check, and then died 14 months later of a brain metastasis. The oldest case was in a man, age 68, who had a radical, complete extirpation of the parotid gland and is alive to-day, ten years later.

In four of the cases, a small tumor had been noted for a number of years, which then suddenly began to increase in size. In three cases, a preoperative diagnosis of malignancy was made; in the remaining six, a cyst or mixed tumor was diagnosed. One of these, a boy, age 14, was operated upon with a diagnosis of sebaceous cyst, but at operation it was found to be an encapsulated tumor within the parotid gland. Pathologic diagnosis was a squamous cell carcinoma arising in a mixed tumor. This patient is now clinically well, eight years after operation.

Two of the nine cases were not operated upon, as the condition was so far advanced that operation was impossible. Biopsies were taken in these cases and diagnosis confirmed pathologically. One of these was the child with sarcoma of the parotid, previously referred to. The other was a patient, age 65, who had a number of roentgen ray treatments, and was then lost track of, probably having died.

Of the remaining seven cases, the tumor was removed primarily in each instance. Two of these cases were lost track of, one died following operation, in whom the tumor had extensively invaded the surrounding tissues. One patient died eight years after the primary excision of the tumor from the parotid gland. This patient had local recurrences involving bone and surrounding tissues. Irradiation did not hold this in check and the patient finally died. Roentgenologic examination of his chest shortly before death did not reveal pulmonary metastases such as Doctor MacFee has shown. As a matter of fact, chest roentgenograms were taken in only two of our nine cases, and both of these were negative.

The remaining three cases operated upon are alive and well, one ten, another eight years after operation, and the third, a recent case. One of these was a man, age 68, who had noticed a mass in the region of the right parotid gland of six months' duration. There were a number of masses, which impressed one as being lymph-nodes, either tuberculous or malignant. On April 5, 1928, the main tumor mass was removed from the gland, and included the lower pole of the parotid which contained the smaller nodules. Pathologic diagnosis showed these masses to be diffuse adenocarcinoma of the parotid. Three weeks later, therefore, under colonic ether-oil anesthesia, the entire parotid gland, with overlying skin surrounding the previous scar, was removed with a block dissection of the cervical lymph nodes, including the submental, submaxillary, omohyoid, carotid, posterior digastric and posterior deep chain groups of nodes. These nodes were removed in one mass with the parotid gland, and a pedicle flap from the posterior portion of the neck was made use of to close the defect in front of the ear. Pathologic diagnosis showed extensive areas of tumor, deep within the parotid and infiltrating the previous operative scar. No lymph nodes were found to be involved. On February 7, 1929, a strip of fascia lata was placed under the eye, from the inner canthus high up onto the parietal portion of the scalp. On December 16, 1931, a strip of fascia data was placed from the zygomatic arch to the angle of the mouth, hooked around the orbicularis oris muscle and brought back to the zygomatic arch. These two fascia lata strips have helped quite materially in overcoming the effects of the facial paralysis, and at least have formed a sling which partially prevents the flapping of the flaccid cheek when the patient talks. Some authors have made use of strips of temporal muscle turned down and fastened to the angle of the eye and angle of the mouth to overcome the paralysis. This patient has remained clinically well for ten years and is now 78 years of age.

In a recent unusual case of papilloma arising from a duct within a cyst of the parotid gland, Doctor James Ewing expressed himself that irradiation was apparently not the method of choice in the treatment of carcinoma of the parotid gland.

According to our small group of cases, it seems that carcinoma arising in a mixed tumor seems to stay well with local excision, while diffuse adenocarcinoma arising from the ducts of the gland is apparently best handled by radical extirpation of the entire gland with the accompanying lymph nodes.

DR. WILLIAM F. MACFEE (concluding) said, in regard to ligation of the jugular veins, that it had not been done in any of the cases he reviewed. It is a suggestion which might be taken into consideration because of the frequent metastases to the lungs, a danger which has not been generally appreciated. He said he certainly had not suspected that anything like 30 per cent of the cases of salivary gland carcinoma would ultimately develop lung metastases. When it is realized that only 11 cases had roentgenograms of the chest, and that eight of these showed metastases, the probability is that an even greater number of the series had thoracic involvement.

Regarding the procedure, when a benign tumor has been anticipated but malignancy is discovered, Doctor MacFee said that if complete removal would involve destruction of the facial nerve, and he had not obtained consent of the patient beforehand, he would desist for the time being. It is frequently impossible to determine the character of a tumor before operating. In response to Doctor Hanford, Doctor MacFee said that, whereas, these tumors may not be encapsulated in the pure sense of the word, many of them do have a fibrous covering which is described by the pathologist as a capsule and which to most of us is indistinguishable from a capsule.

One hint with regard to malignancy: Inclusion of the facial nerve in a tumor is a strong point in favor of malignancy. It is unusual for a benign tumor to actually incorporate the nerve. The parotid gland itself develops, primarily, external to the facial nerve; the vast majority of benign tumors are likewise external to the nerve and tend to push it aside as they develop. Malignant tumors, on the other hand, may actually include it.

Concerning recurrence after complete removal: If a tumor first comes under observation as a recurrence, there is frequently no way of knowing exactly what was done at the original operation. Sometimes, however, there is recurrence at the site of a tumor which is known or believed to have been completely removed. In such a case the possibility of malignancy should be seriously considered.

MIXED TUMORS OF THE SUBLINGUAL GLAND*

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MIXED tumors of the sublingual gland, strangely enough, considering their frequency in the parotid, are very rare. Dr. B. R. Shore[1] informs me that, in the files of the Pathologic Department of St. Luke's Hospital, during the past 40 years, there are recorded 135 mixed tumors of the salivary glands, of which 119 were parotid, 15 submaxillary and but one sublingual, which is herewith reported.

The history of the patient herewith reported is reminiscent of that of Brunschwig[2]—a woman, age 60, who died with extensive local destruction of the floor of the mouth and mandible and metastases to lungs and pleura due to a mixed tumor. The original growth in the right sublingual gland had been removed 19 years previously.

Brunschwig, when he published the case cited above, in 1930, had been able to find but two others in the literature up to that time, which seemed to him to be properly authenticated. Since then a number of cases have been reported, as summarized in Table I.

TABLE I

SUMMARY OF REPORTED CASES OF MIXED TUMORS OF THE SUBLINGUAL GLAND

Author	Malignant	Recurrent	Benign	Not Stated	Total
Brunschwig[2]	1		2		3
Greenberg[3]†				1	1
Patey[4]		1			1
Eschweiler[5]	1				1
Ahlbom[6]	1		1		2
Vergoz and Salasc[7]			1		1
McFarland[8]		1			1
Smith	1				1
	4	2	4	1	11

† Although Greenberg's[3] article appeared one year before that of Brunschwig,[2] the reference in the Quarterly Cumulative Index appeared some time afterward; it is, therefore, included.

The frequency of occurrence of mixed tumors of the sublingual as compared to those of the other salivary glands may be judged from the statistics in Table II.

Case Report.—E. C., female, white, married, age 31, was admitted to St. Luke's Hospital in March, 1924. Three years previously, she had noted a swelling in the floor of the mouth which had been lanced on several occasions. Examination revealed a nodu-

* Presented before the New York Surgical Society, May 11, 1938. Submitted for publication August 4, 1938.

TABLE II

COMPARATIVE INCIDENCE OF MIXED TUMORS OF THE SUBLINGUAL AND PAROTID GLANDS

Greenberg [3]†	1 of 30	Ahlbom [6]	2 of 202
Patey [4]	1 of 45	McFarland [8]	1 of 297
Chen and Loucks [9]	0 of 37	Shore (St. Luke's)	1 of 135
Martin and Elkin [10]	0 of 24		

6 of 770 = 0.8 per cent

lar thickening of the right sublingual gland, which was removed through an incision in the floor of the mouth. The operative diagnosis was chronic inflammation of the gland, but the pathologic examination showed a mixed tumor, presumably of the sublingual gland, although no normal gland tissue was found in the sections (Fig. 1).

About four years later, June, 1928, she was again operated upon for a local recurrence. A second recurrence was not long in making its appearance, and she was readmitted to the hospital a third time, in December, 1929, at which time there was present a hard, irregular mass, 2.5 cm. in diameter, attached to the mandible. Roentgenologic examination showed bone involvement of the right side of the jaw close to the symphysis.

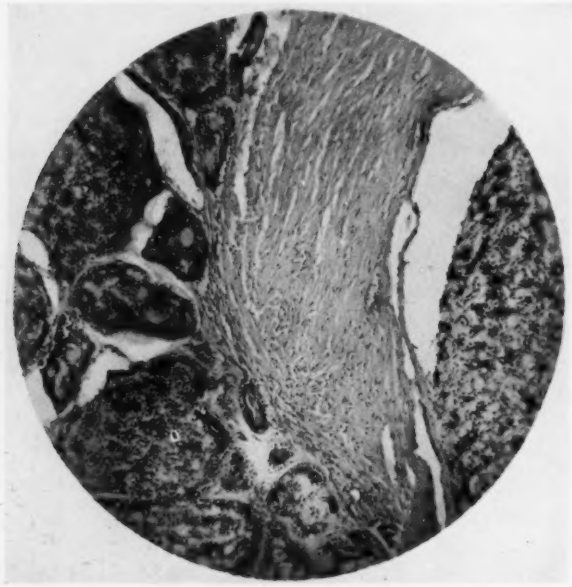

FIG. 1.—Photomicrograph of mixed tumor of the sublingual gland.

The chest was negative. At operation, the mandible was split and the floor of the mouth on the right side dissected out including periosteum and underlying bone at the site of attachment of the tumor. The pathologic diagnosis at this time was adenocarcinoma of the sublingual gland, recurrent. The morphology was the same as that of the tumor previously removed. There was bone and muscle involvement.

In August, 1932, she was again seen at the hospital. Examination showed a small, hard swelling on the left side and two on the right side, below the mandible. A roentgenogram disclosed disease in the jaw bone. Further surgery was considered inadvisable and she was referred to the Radiotherapy Department where she has been under treatment ever since. During the period through 1936, she received an average of 2,000 r. per year. This was increased to 5,000 r. in 1937. Thus far in 1938, she has received 1,600 r.

In October, 1937, she reported that there had been considerable pain in the jaw for two months and a discharge from the floor of the mouth. The chin was swollen and reddened. Roentgenologic examination of the chest showed metastases in the lungs, although there were no pulmonary symptoms (Fig. 2).

During the past winter the mandible sequestrated, with relief of pain and healing of the sinus. In the past few weeks, however, pain has appeared in the left side of the chest, which may be due to the pulmonary or pleural metastases. There is induration and thickening of the floor of the mouth but no lymph node involvement. The patient's general condition is fairly good. She is thin, but only six pounds under her usual weight. (This patient is included in the series of cases forming the basis of Dr. W. F. MacFee's paper on "Malignant Tumors of the Salivary Glands." ANNALS OF SURGERY, 109, 481, April, 1939.)

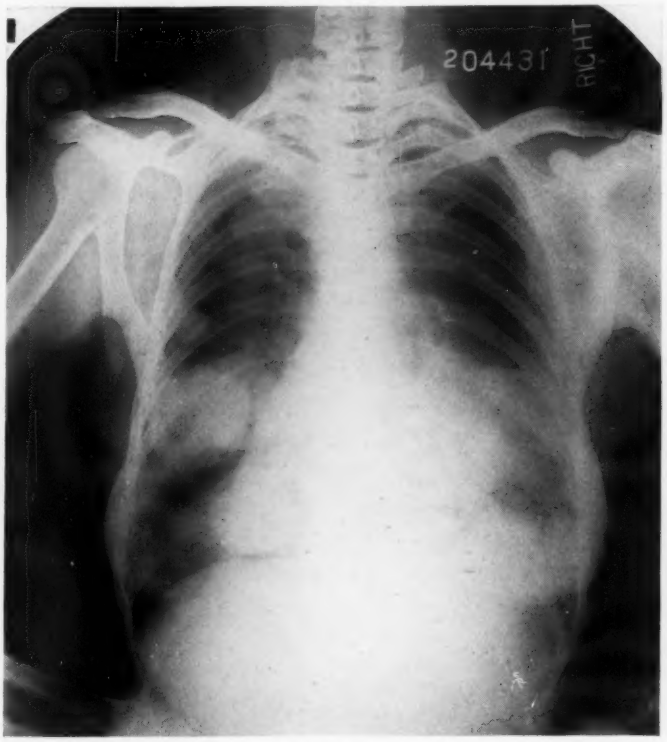

FIG. 2.—Roentgenogram showing metastases to the lungs from a mixed tumor of the sublingual gland; 13 years after first operation.

Points of interest in this case are: (1) The location of the original tumor, which, although not absolutely proved, seems from the evidence to be reasonably attributable to the right sublingual gland; (2) the duration of the disease, now 17 years; (3) the absence of demonstrable lymph node involvement; (4) the pulmonary metastases; and (5) the restriction of local growth since beginning roentgenotherapy, almost six years ago.

SUMMARY

A case of mixed tumor, presumably of the right sublingual gland, which has proven clinically to be of a low grade of malignancy, is presented. The

patient is alive, with pulmonary metastases, 17 years after the tumor was first noted. The recent literature has been reviewed and 11 cases of mixed tumor of the sublingual gland, including the one reported, assembled. Four of these were malignant. The incidence of sublingual among salivary gland mixed tumors is 0.8 per cent.

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ESOPHAGOGASTROSTOMY FOR CARCINOMA OF THE ESOPHAGUS

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ONE of the most interesting and important chapters in the development of gastro-intestinal surgery is that dealing with the esophagus and cardiac portion of the stomach. This part of the gastro-intestinal tract has, from many angles, defied surgical attack: First, because a transpleural exposure was imperative. With the development of a technic placing intrathoracic surgical procedures on a sound basis, plus modern methods of administering anesthesia, the first strategic point has been attained. Second, the absence of a serous coat to the esophagus, once it has been freed from its retropleural, or mediastinal location, has made anastomosis for reestablishing the continuity of the gastro-intestinal tract a hazardous procedure. The fact that this difficulty has been overcome in a few successful cases is a source of great encouragement. It is, therefore, predictable that this technic will soon become perfected and standardized, placing the operation on an acceptable basis. Third, a further difficulty that has prevented an otherwise successful issue is postoperative mediastinitis. This, too, in some cases, has been overcome by a simple surgical principle; namely, meticulous care in freeing the esophagus and making no effort to close the space after mobilizing the necessary portion, plus adequate drainage.

The accomplishments of Lilienthal,[3] Garlock,[7] Eggers,[5, 8, 11] Adams,[9, 10] Marshall,[12] Brunn,[6] Ohsawa,[13] Penberthy and Benson,[14] and others have added materially to the development of a sound technic and have stimulated interest in this most difficult problem. At present, the surgeon's greatest handicap, in successfully dealing with these cases, is the tardiness with which they are brought to his attention, or the Chauvinistic complex from previous experience, making palliative treatment seem preferable. It is only by the publication of exact and true statements of efforts in this direction that this handicap can be eliminated. Under present conditions it seems worth while, therefore, to report the appended case in detail.

Case Report.—Hosp. No. 205-505: C. T., female, age 46, was admitted to the New York Hospital, May 27, 1938, with the history of having first noted difficulty in swallowing certain foods in November, 1937, accompanied by a considerable loss of weight and strength. A diagnosis of a lesion at the esophageal-cardiac junction was made after roentgenologic examination (Fig. 1). Radical treatment, however, was not advised. In April, 1938, the symptoms had greatly increased; and loss of weight and strength were progressive. She consulted Doctor Prewitt, who hospitalized her in the Park East Hospital, April 26, 1938, Case No. 24533. Preoperative treatment was immediately instituted. Not only had there been a loss of 15 pounds in weight and the development of a moderately severe secondary anemia but, as in all cases of stricture of the esophagus,

Submitted for publication September 22, 1938.

the stomach had become so contracted that it held but four ounces. A Levine tube was passed through the nostril, and regular feedings of a balanced diet, including a proper vitamin content, were administered. The quantities given with each feeding were gradually increased, not only to restore the patient's physical condition, but also to dilate the stomach to a more normal size, so that a sufficient amount of the viscus could eventually be delivered into the left thorax to permit resection and anastomosis without ten-

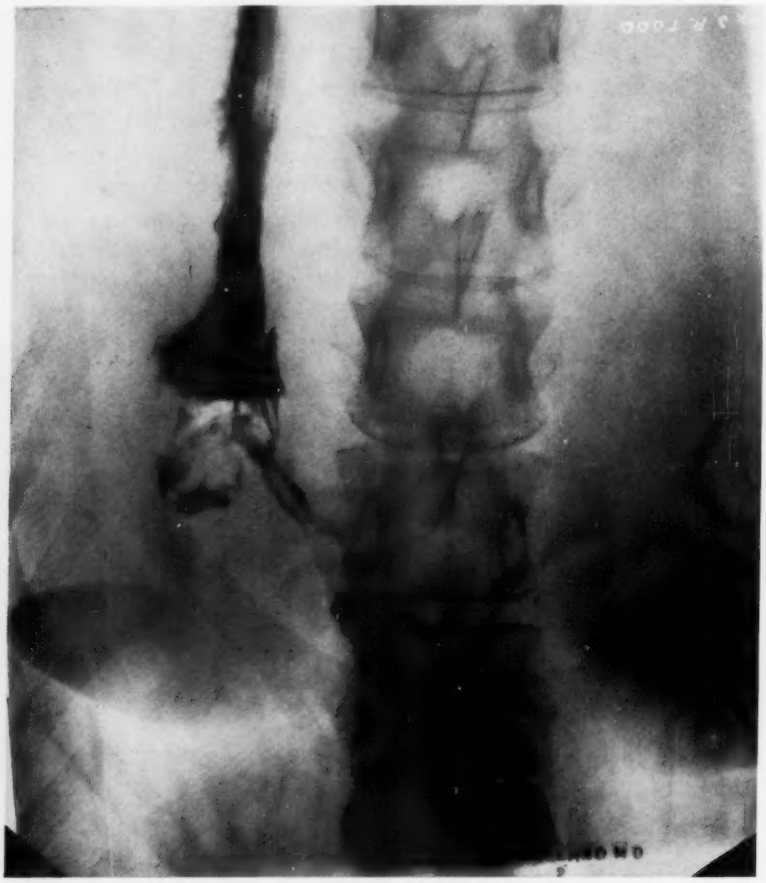

FIG. 1.—Roentgenogram showing slight dilatation of the lower esophagus with the greater amount of tumor tissue in the stomach just below the esophagus.

sion. The patient was gradually forced to take 6,000 calories per day in repeated 10 ounce feedings. The weight return and the redilatation of the stomach was a slow process.

When admitted to the New York Hospital, the patient appeared well nourished; blood count normal; Wassermann negative. Weight 106 pounds, a loss of 10 pounds from her greatest weight. Her stomach would receive 10 ounces without causing undue discomfort.

Operation.—June 5, 1938; Doctor Bohrer: Anesthesia was induced with a basal dose of avertin supplemented by intratrachael cyclopropane and oxygen, by Dr. George van Gilluwe; there was good relaxation and the anesthetic was well tolerated. An eight-inch incision was made over the left eighth rib from the angle forward (Fig. 2). A left pneumothorax had been induced 10 days preoperatively and there was no disturb-

ance of pulse or respiration when the rib was resected and the thorax opened. The left pulmonary ligament was divided, allowing the lung to retract from the operative field. No metastatic nodes could be palpated in the mediastinum. A hard mass could be felt through the diaphragm in the region of the cardia.

A four-inch radial incision was then made through the left diaphragm, starting one inch lateral to the hiatus. Through this incision the operator was able to palpate and explore the abdominal viscera. The tumor was estimated to be three inches in diameter. No enlarged nodes were felt in the gastrohepatic omentum. The tumor was not adherent; the liver was normal to palpation. The ligament of Treitz was located and a long loop of jejunum was easily delivered through the diaphragmatic wound. When the examining hand was removed, the spleen herniated through the incision. The abdominal viscera were easily reduced and could be held in place by a small pad. The phrenic nerve was located and blocked with novocain. An incision was made over the esophagus

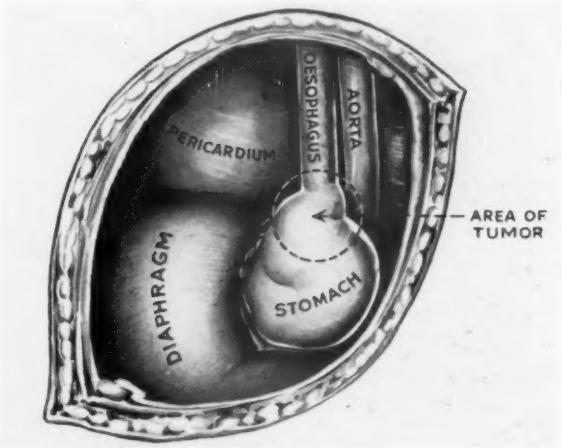

FIG. 2.—Thoracic cavity opened over the site of the eighth rib. Esophagus has been mobilized; diaphragm incised and stomach delivered into thoracic cavity.

and four inches of it were mobilized from the mediastinum. A gauze pack was immediately introduced into this space to prevent bleeding and protect the space from being soiled. The diaphragmatic incision was carried down through the hiatus, allowing the operator to free the entire lower four inches of the esophagus. At this stage of the dissection the vagus nerves were observed, together with the plexus about the esophagus and upper stomach. It was necessary to divide the left vagus. The most difficult part of the operation was experienced in clamping and dividing the left half of the gastrohepatic ligament and the division of the coronary artery. This, however, was accomplished without accident and the tumor and cardia were delivered into the thorax. Due to the contraction of the stomach, it was difficult to deliver a sufficient amount of it to allow complete removal of the tumor and permit an anastomosis of the esophagus to the stomach. The original plan had been to close the stomach aperture, made by resection of the tumor, then roll the greater curvature up to the cut end of the esophagus and make a small incision to fit the size of that viscus on the anterior gastric surface. The small size of the stomach, however, would not allow this procedure. The tumor, therefore, was resected; and starting at the greater curvature, the stomach was closed down to an aperture just large enough to permit anastomosis with the esophagus (Fig. 3). The anastomosis was made with a very fine, curved intestinal needle, carrying a fine silk thread. Two layers of interrupted sutures were used. A careful approximation of the mucosa was accomplished. The posterior suture line was reinforced by a fat pad

covered with pleura that is usually found at the diaphragmatic-mediastinal angle. The anterior suture line was reinforced by a third layer of stomach to the esophagus. The esophageal wall was a firm, thick layer of longitudinal muscle. There was no trouble in approximating the surfaces and no tearing of the muscle by the suture occurred. When completed, the anastomosis appeared strong, there was no tension, and it seemed perfect. The packing was removed from the mediastinum; no bleeding was observed and no attempt was made to close it.

The peritoneal cavity was closed by interrupted suture of the cut edge of diaphragm to the stomach. A siphon drainage tube was introduced through an intercostal stab wound and the thorax was closed in the usual manner. The patient was given 1,000 cc. of saline solution and 500 cc. of citrated blood during the three hour operation. She was returned to her room in good condition; there was no secondary shock.

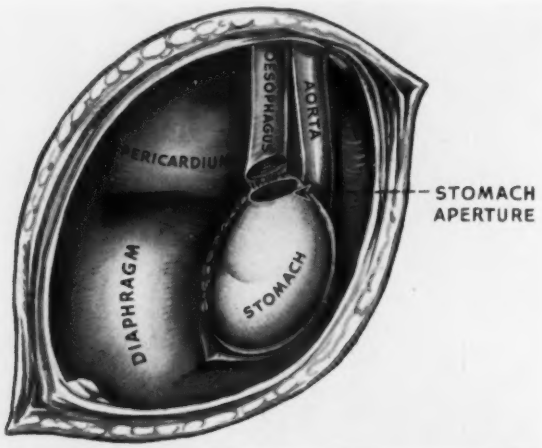

FIG. 3.—Suture line of stomach after resection. Posterior suture line of esophagogastrostomy.

Subsequent Course.—The first night the patient's temperature reached 101°, remaining below that during the ensuing week. There was a slight amount of serosanguineous drainage during the first 24 hours and none the following day. The Levine tube, which had been passed into the stomach just before the final closure of the anastomosis, was used as a "gas fistula" for the first three days. Later water and food were introduced into the stomach through this tube.

The patient was given 3,000 cc. of 5 per cent glucose in saline every 24 hours. However, she developed slight edema of the feet, necessitating a reduction of the saline. Sufficient insulin was administered to prevent glycosuria. There had been no postoperative intestinal disturbance, and no distension or pain. The bowels moved on the fourth postoperative day following the administration of cascara.

On the sixth postoperative day, the patient was permitted to swallow water and a slight drainage around the intercostal tube was noted. The chest was aspirated but nothing was recovered. On the seventh day, some buttermilk was unintentionally swallowed; a fistula was demonstrated to be present, as milk was noted in the drainage. A Witzel type of jejunostomy was immediately performed and all feedings were administered through the jejunum. An interesting intestinal phenomenon then developed: The patient had been moderately constipated preoperatively and during the early postoperative period, but with the introduction of peptonized milk, gruel and similar material into the jejunum, a marked hyperperistalsis was initiated, often resulting in an evacuation immediately after the feeding. This was annoying and troublesome to the

patient, but it was possible, however, to keep her in fair food balance for the ensuing two and one-half weeks by jejunal feeding.

Immediately following the development of the fistula, the lower angle of the chest wound was opened for four inches, giving adequate drainage and permitting direct observation of the fistula and anastomosis by introducing a small electric light. This observation was repeated frequently, and it was obvious that the fistula was closing. On the ninth postoperative day, the patient was allowed to sit up in bed, the dressing was removed and she was given water by mouth. About one-half of the fluid intake was recovered through the fistula, but on successive days the quantity recovered became less and less. Charcoal tablets, given by mouth, were, at first, returned through the fistula in considerable amount; later, practically all returned in the stools. On the twenty-sixth postoperative day, she was allowed solid food; a very small amount being recovered through the fistula. On the evening of that day, the patient entertained her family and friends, discussed household details and plans for returning to her home. She was in excellent condition. That night, she received .025 Gm. of sodium luminal by hypodermic as a sedative. There was considerable "hangover" the next morning but the patient took a small breakfast, was out of bed, and seemed normal except for being sleepy. She returned to her bed at 11 A.M. and under the writer's observation suddenly started muttering, became unconscious, and developed a rapid pulse with cyanosis and dilated pupils. Her condition improved, only to have a second attack at 4 P.M. She expired at 7 P.M. *Clinical Diagnosis:* Cerebral embolism. One must, however, question the late effect of sodium luminal, although the patient had repeatedly taken usual doses of phenobarbital without distress.

The untimely death of this patient left unsolved the ultimate outcome of the gastro-esophageal fistula. Judging from its progress up to the time of death, there seemed but one conclusion; namely, complete closure. However, the autopsy disclosed a larger defect in the mucosa than in the muscle wall. The writer believes, however, that it would ultimately have healed completely.

It is interesting to note the slight degree of suppurative pleurisy which developed, and the fact that even in the face of a fistula, no mediastinitis was present. The temperature and pulse curve had been normal for one week prior to her death.

Pathologic Examination.—Gross: Doctors Moore and Krumdieck. No. 9336: Specimen is the terminal 2 cm. of esophagus and proximal 4 cm. of stomach. The lumen of the cardio-esophageal angle is markedly constricted and does not permit passage of the little finger. Situated at the angle is a firm, annular tumor mass which completely encircles the stomach and esophagus at this point. Its inner aspect presents multiple discrete and confluent papillary excrescences, zones of ulceration, which give the summit a cauliflower-like appearance (Fig. 4). The tumor infiltrates the wall and extends approximately to a point 2 Mm. below the sectioned portion of the esophagus. Distally, the tumor infiltrates approximately 2 cm. above the cut margin of the cardia. On section through the tumor there is disclosed a diffusely pearly-gray infiltration in which are noted innumerable lemon-gray granules. The architecture of the region of infiltration is completely obliterated. The gastric mucosa, other than the portion which presents the tumor, shows diffuse hemorrhagic engorgement. There is a small linear, 1 x 0.5 cm., portion of esophageal mucosa which shows no evidence of gross involvement. The serosal aspect of the specimen is nodular. The nodules are flat, and average 2 to 4 Mm. in diameter. There are several lymph nodes which show markedly degenerated surfaces on section and which exude a milky substance on pressure.

Microscopic.—Sections through the tumor masses present widely infiltrating, irregularly anastomosing cords and discrete islands of atypical squamous cells. The cells vary markedly in staining affinity; some present markedly hyperchromatic nuclei, while other nuclei are vesicular and pale. The cells vary markedly in size. There are frequent giant-sized cells found. There is occasional tendency to pearl formation and suggestive

keratinization. The sections also reveal a very prominent degree of necrosis, fibroblastic proliferation and infiltration with young organization tissue, and foci of inflammatory cells. The carcinomatous infiltration is so wide as to completely obscure the basic markings of the section. In no portion, of those areas examined histologically, are the cells of the gastric epithelium recognized. The regional lymph nodes show evidence of extensive involvement by the atypical squamous cells. There are also lymph nodes included in the section which show no metastatic involvement but marked hyperplasia and vascular engorgement.

Pathologic Diagnosis: Immature, stenosing, annular, ulcerating squamous cell carci-

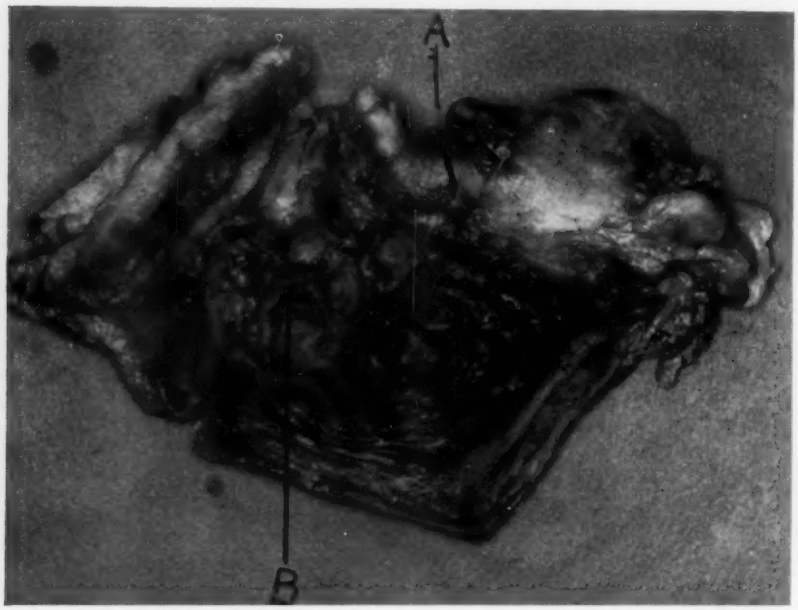

FIG. 4.—Resected specimen of esophagus and stomach cardia. A. Constricted esophageal orifice. B. Cauliflower mass which completely encircled the esophageal orifice and cardia of the stomach.

noma of the esophagus with infiltration of the stomach and metastatic involvement of the regional lymph nodes.

Significant Autopsy Findings

(1) At the site of the anastomosis the mucosa had failed to heal by primary union in two distinct areas. Both of these defects communicated with the esophageal fistula leading into the pleural cavity.

(2) There was a very small metastasis to the liver and also to the small lymph nodes in the gastrohepatic ligament.

(3) Sections at the site of the anastomosis showed no tumor cells.

(4) There was a fibrinopurulent pleurisy of the left pleural cavity.

(5) The remainder of the gastro-intestinal tube was normal except that the portion of the stomach lying below the diaphragm was markedly contracted, being one and one-half inches in diameter.

(6) No gross anatomic lesion of the brain was found.

DISCUSSION.—Several questions naturally present themselves:

(1) Why did the fistula develop; and would it eventually have healed?

(2) Would the lung have reexpanded after prolonged collapse with an open pyothorax?

(3) Was it proper to explore through the thoracic route or should the operability have been determined by abdominal exploration?

(4) What is the physiology of the excessive persistalsis following jejunal feedings?

(5) Had the exploration revealed metastases to the liver and to local lymph nodes, as described in the autopsy protocol, was resection indicated?

(1) The answer to the first question must, necessarily, be largely speculative. Three facts are definitely known: First, that both stomach and esophagus were viable at the time of the anastomosis; second, meticulous care was taken to approximate the mucosa; third, at the autopsy, no tumor cells were found at the site of the dehiscence. In spite of these facts, the mucosa did not heal per primam. The probable explanation is that the blood supply to the mucosa on both sides had been markedly reduced (a) by the operative procedure; (b) by the slightly angulated position in which they were left after the anastomosis, the stomach being pulled through the diaphragm and the esophagus removed from its normal mediastinal position; (c) a third factor must also be considered; while the Levine tube served admirably as a "gas fistula," the presence of a foreign body in close approximation to any suture line is always objectionable, particularly where the blood supply is questionable. The writer believes, however, the Levine tube was in no small way responsible for this defective healing. A simple gastrostomy would better have served all requirements. The pull of the powerful longitudinal muscles of the esophagus during deglution (a preoperative fear) could not have had much influence on the mucosal union, as the muscle suture line held satisfactorily. An observation made on the exposed portion of the esophagus by means of the above described electric light demonstrated the marked peristaltic action of this powerful muscle.

By limiting the amount of material passing through the fistula, and not introducing food into the stomach that would stimulate secretion of digestive juices, erosion of the fistula was avoided; from direct observation it is fair to conclude that the fistula eventually would have closed.

(2) At the autopsy, the left lung was found markedly collapsed. It did not crepitate. The visceral pleura was not markedly thickened. It is conceivable that with a closed sterile pneumothorax this lung would have reexpanded. If not, the right lung probably would have hypertrophied and herniated into the left pleural cavity to fill the space. If the pleurisy could not be controlled and a sterile pneumothorax secured, thoracoplasty would have been imperative.

(3) In answer to this question, the writer has a definite belief; namely, thoracic exploration is the route of choice. (a) Contrary to general belief, the thoracic route causes no greater shock than abdominal exploration, but more time is required in opening and closing the wound. (b) Exploration is much more adequate since the thorax as well as the abdomen can be satis-

factorily examined. (c) If operable, the incision permits immediate procedure. (d) It is more difficult to determine operability by the abdominal route, hence many operable cases would be rejected. From present experience, the thoracic route for exploration of operability is by far the more acceptable.

(4) The intestinal hyperperistalsis induced by jejunal feeding is an interesting physiologic fact. It has been observed many times and seems not to be unusual. It is probably the same reaction that is noted when a quart of warm saline is given on an empty stomach to a person suffering from constipation. In this instance, the warm solution leaves the stomach at once and when it reaches the jejunum hyperperistalsis ensues followed by evacuation. It has also been noted following complete gastric resection when the continuity of the gastro-intestinal tract is reestablished by an esophagojejunostomy. In the latter instance, this difficulty is gradually overcome.

It will be noted that during the exploratory phase of the above described operation, the jejunum was delivered into the thorax. This was done to assure the operator an alternative in case a union of esophagus and stomach could not be made without tension. Judging from experimental work on dogs, this would not be a desirable procedure on a human.

(5) This, of course, is a debatable question. The European surgeon undoubtedly would answer in the affirmative, since the metastases were so small and the original lesion so productive of discomfort. Given a small metastatic lesion in a silent area, the writer is inclined to believe that the removal of the primary malignant lesion, where it causes or will cause severe suffering, is the proper course to follow.

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DUODENAL STASIS

CLINICAL AND EXPERIMENTAL OBSERVATIONS

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DUODENAL stasis, or chronic duodenal ileus, a condition remarkable for the number and variety of clinical symptoms attributed to it, is also one which is variously defined in the literature. This diagnosis is made by some authors when the opaque medium seems to hesitate for several seconds, as it were, before entering the distal part of the duodenum or the jejunum[20]; yet it is known that such delay may occur when the stomach empties rapidly,[2, 6] owing, for example, to hunger or to the action of purgatives.[2] Other writers consider that, besides the delay, there should be writhing or pendulum peristalsis which is "quite characteristic of obstruction"[18]; it is known, however, that this type of peristalsis occurs in duodenitis; that it may be found in affections of the gallbladder,[6, 7] the pancreas,[6] and the appendix[6, 7]; that it is even seen in healthy persons[4, 6] in other words, that it does not necessarily indicate obstruction. Taking a more conservative view, duodenal stasis implies widening of, and long lasting retention in, the dependent duodenum[7, 9]; but Barclay[2] has found this to occur in people who were not conscious of any disorder; wherefore, he concludes that symptoms might have been ascribed to what is, in reality, a normal but unusual variation of the duodenal mechanism. In its practical consequences, this view differs radically from that of a majority of authors, who advocate medical or surgical treatment, under the assumption that duodenal stasis is the expression of some kind of obstruction.

This divergence of opinions about the clinical significance of a mechanism believed to be pathologic is not surprising if one considers how little is known about the normal physiology of the duodenum; for this segment, which is subject normally to influences from various organs and of various kinds, may considerably alter its function and, hence, its appearance during different phases of digestion. If present descriptions of normal duodenal activity differ, it is probably for this reason; nevertheless, all of the descriptions may be correct, as each may fit one special type or phase of gastric and intestinal digestion—the type of peristalsis varies individually, with the kind and quantity of the opaque meal given, and with certain technical factors of the roentgenologic observation.

Physiologic Data.—The passage of an opaque medium through any part of the digestive tract is obviously dependent on, and to some extent controlled by, the condition of the adjacent sections. The passage through the duodenum is influenced by the following factors at least: The relation in size and capacity

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between stomach and duodenal cap; the liquidity of the gastric contents; the rate of passage through the cap; the condition of the duodenal mucosa; and, naturally, the pyloric mechanism. These factors, again, are made variable by the chemical processes of digestion.

In examinations of 300 healthy students, the following type of duodenal activity has been found to be common, it being understood that in the physiology of digestion there is no such thing as one single normal mechanism: After having passed through the pylorus, the opaque medium remains for a number of seconds in the cap,[1] at the tip of which it seems to become arrested. Incidentally, this is the reason why the cap is so easily visualized in healthy subjects. By a contraction, wave-shaped or more tonic, which proceeds from the tip of the cap towards the pylorus,[3] the opaque medium is then driven into the descending duodenum as though by the action of a bellows.[3] While being thus moved on, the opaque medium is evenly spread over the duodenal mucosa, thereby producing the fragmented or "feathery" aspect of the normal mucosal relief. During this time, the cap may fill again, and the cycle repeat itself; but it is more common for the pylorus not to relax until all or most of the opaque medium has been moved on into the third or fourth duodenal portion, either by a "stripping" contraction progressing smoothly from the tip of the cap downward, or by what appears to be the activity of the muscularis mucosae (not, of course, by the activity of the valleculae conniventes, as recently stated[18]).

At the very beginning of gastric evacuation, as well as during its second half, the entire mechanism is less regularly timed than at the period of active gastric peristalsis, the latter being normally most marked about ten minutes after ingestion of the opaque medium. More information on normal physiology can be obtained by giving some opaque medium at different intervals after ingestion of a normal meal containing fat and protein. Provided gastric acidity is normal, very little of the gastric contents passes through the pylorus during the first hour; small amounts accumulate in the cap for considerable periods, up to 45 minutes, after which they pass very rapidly through the entire duodenum. But, after about three hours, gastric evacuation becomes more rapid, and the passage through pylorus and cap is then very similar to that observed about ten minutes after ingestion of plain barium sulphate suspension, though usually somewhat slower. When the cap is small, either congenitally or owing to scars and fibrosis, the opaque medium evacuated during a normal pyloric relaxation overfills the cap, with the result that parts or all of the barium proceed immediately into the dependent duodenum. Similarly, a tonic contraction of the cap, as observed in duodenitis,[12] or motor irritability, as in duodenal ulcer, produces a diminution in capacity of the cap, with similar results. The relation between the cap and the stomach may also be altered in the presence of permanent patency of the pylorus, *e.g.*, in hunger, or in carcinoma infiltrating the pylorus; and a continuous flow into the jejunum is then not uncommon. When the duodenal mucosa is swollen, various alterations of the passage are observed and frequently associated with pylorospasm; in the absence of

FIG. 1.—(A) Normal duodenum. Arrest at the tip of the cap; "feathery" mucosa in dependent part. (B) Duodenal stasis; valleculae conniventes permanently seen. (C) Atony of duodenum during gallbladder colic.

the latter, however, rapid passage through the cap is commonly though not invariably noted.

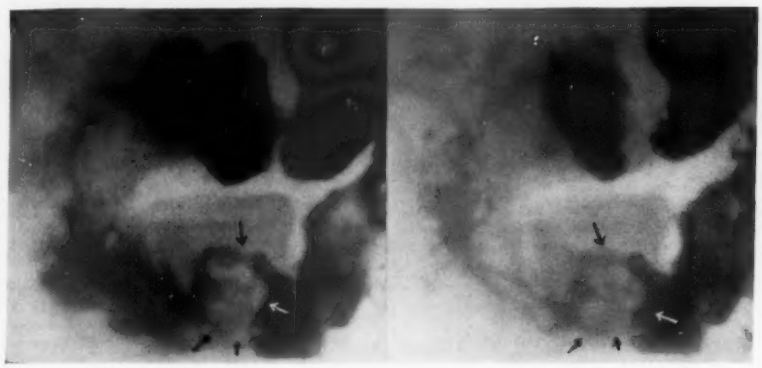
Increase of fluid in the stomach, both by pathologic hypersecretion or retention and by the physiologic increase which often occurs towards the end of gastric evacuation, is usually associated with very rapid passage through the upper duodenum, provided the pylorus is not spastically closed; but even in the presence of pylorospasm, rapid passage through the duodenum may be observed under favorable conditions during the short periods of pyloric relaxation.

Unpublished experiments with various types of food suggest that the abnormal duodenal peristalsis observed in certain biliary diseases[15] is related to the amount of fat admixed with the opaque medium; although the results are not yet conclusive, they are here mentioned as a suggestion that extra-intestinal conditions may at times influence the duodenal mechanism.

In all the conditions above discussed, irrespective of their being physiologic or pathologic, rapid passage through the duodenal cap is often associated with a delay of the passage through the dependent duodenum. The barium which, in these cases, seems to fall through the descending portion, may either collect at the lower duodenal knee (*genu inferius duodeni*), whereby the latter appears to be temporarily somewhat widened; or it may become arrested in the lower horizontal loop (*pars horizontalis inferior duodeni*) by what appears to be a circular tonic contraction. While in the former case, there is, in general, no marked peristalsis, writhing and surging are common in the latter condition. In either case,

the opaque medium is moved on into the jejunum after a period of, say, from two to ten seconds. Excepting for peristaltic waves, nothing changes the aspect of the normal "feathery" mucosal pattern; only occasionally, for a second or two, may the valleculae conniventes emerge, as it were, into the mucosal relief.

Clinical Observations.—From the mechanism above described, duodenal stasis differs in degree rather than in kind: The widening of the dependent portion persists throughout indefinite periods of observation; the valleculae conniventes are permanently seen in the region of stasis, whereby the normal fragmentation of the medium disappears; and the barium accumulates in a pool for periods extending over hours. In the upright position this pool may be smoothly outlined, the valleculae appearing to be flattened out by the weight of the stagnant opaque medium; but in recumbency, when the duodenum is less overfilled at one place, the valleculae are recognizable either in relief or,



A B

FIG. 2.—A and B: Duodenal cycle in an instance of tumor of horizontal portion (arrows). Note absence of retention.

at least, by the regular indentations they produce in the duodenal contour. Increased or abnormal peristalsis, such as writhing, churning, and surging, may or may not be noted; if present, it is usually more pronounced in the recumbent position.

According to present views, duodenal stasis signifies, in a majority of cases, obstruction of the duodenum by some anatomic process: Intrinsic growth; compression by extrinsic tumors; kinking by periduodenal adhesions; compression by the superior mesenteric vessels (arteriomesenteric occlusion); and megaduodenum.

(1) *Intrinsic Growth.*—This is very rare.[2] In a case of annular tumor recorded by Barclay,[2] retention and dilatation of the duodenum cephalad to the growth were very marked. The author has seen two cases, but neither of them was verified by operation; there was no stasis (Fig. 2).

(2) *Extrinsic pressure.*—Twelve cases of pancreatic tumors (seven verified) and eight cases of various growths causing displacement of, or pressure upon, the duodenum, were studied for duodenal stasis. The duodenal curve was found widened in 11 tumors of the pancreas; the duodenum was flattened

and its lumen slit-shaped in the same 11 cases, and in one case of an enormous right hydronephrosis containing 11 liters of fluid; there seemed to be no flattening in one pancreatic tumor and all the other tumors; retention in the duodenum was found in two cases of pancreatic tumor with flattened duodenum and in one case of retroperitoneal sarcoma, in both of which the valleculae conniventes were permanently seen; but in all the other instances, there was neither retention nor persistence of valleculae, the duodenal relief showing normal segmentation. Hence, there was duodenal stasis in three out of 20 cases of extrinsic compression (15 per cent).

(3) *Periduodenal Adhesions.*—There are two distinct groups: (A) Adhesions in the upper duodenum due to ulcer; (b) adhesions in the duodenum distad to the cap, *e.g.*, to the liver and gallbladder or towards the colon. Only such cases have been analyzed in which adhesions were unquestionable owing to the immobility, deformity, or angulation they produced. Fifteen cases of Group A, and seven of Group B were studied. Briefly, the results are as follows: No duodenal stasis was found in Group B; stasis was present in five cases of Group A; in all of the latter, the passage through the cap was rapid—three times in the presence of an active duodenal ulcer with crater, and twice in the presence of a pipe-shaped deformity of the cap.

(4) *Arteriomesenteric Occlusion.*—This is held to be due to pressure upon the duodenum by the superior mesenteric vessels, when the angle formed by the aorta and these vessels is lessened, and when there is tension on the mesenterium owing to visceroptosis. The acute form occurs as a rule in patients too seriously ill to allow extensive roentgenologic studies. In three cases, where the clinical symptoms and signs suggested this condition, roentgenologic examination showed permanent atony and dilatation of the stomach, with no filling of the duodenum; in two of them, autopsy failed to reveal the presence of any kind of obstruction. This is in accord with observations published by German authors.[13, 19] In the chronic or intermittent form, the roentgenologic findings described in the literature are those of duodenal obstruction; that is, according to the foregoing, indirect, untypical, and ambiguous signs. With an adequate technic, however, the presence of so serious an obstruction should be revealed by the more tangible "direct" roentgenologic signs—in obstruction by a rather large vessel, the filling defect caused by its pressure should be demonstrable. Such a defect, at the left border of the spinal shadow, has been found in four of our cases of duodenal stasis. In two of them, however, there was an active duodenal ulcer, and stasis disappeared when the crater had grown smaller. In the third instance, a woman with amebic colitis, examination in various diameters showed that the fourth part of the duodenum was located much more anteriorly than could be expected in the instance of compression by the mesenteric vessels; and in the fourth case, the defect was so variable in size and localization as to suggest tonic contractions rather than an anatomic compression.

(5) *Megaduodenum.*—Two cases have been seen; in one, a child who died of dysentery, no roentgenologic examination was made; no obstruction was found distad to the enlargement on autopsy. In the second instance, a stout

woman, age 37, stasis was more pronounced than in any other instance observed by us; after passing normally through a cap of average size, the opaque medium collected at the lower duodenal knee, in a pool about one-third the size of the stomach, and it moved on merely by flowing over the level of the pool. The latter remained visible as an isolated filling after the entire tract had emptied itself. No mucosal pattern was demonstrable, and

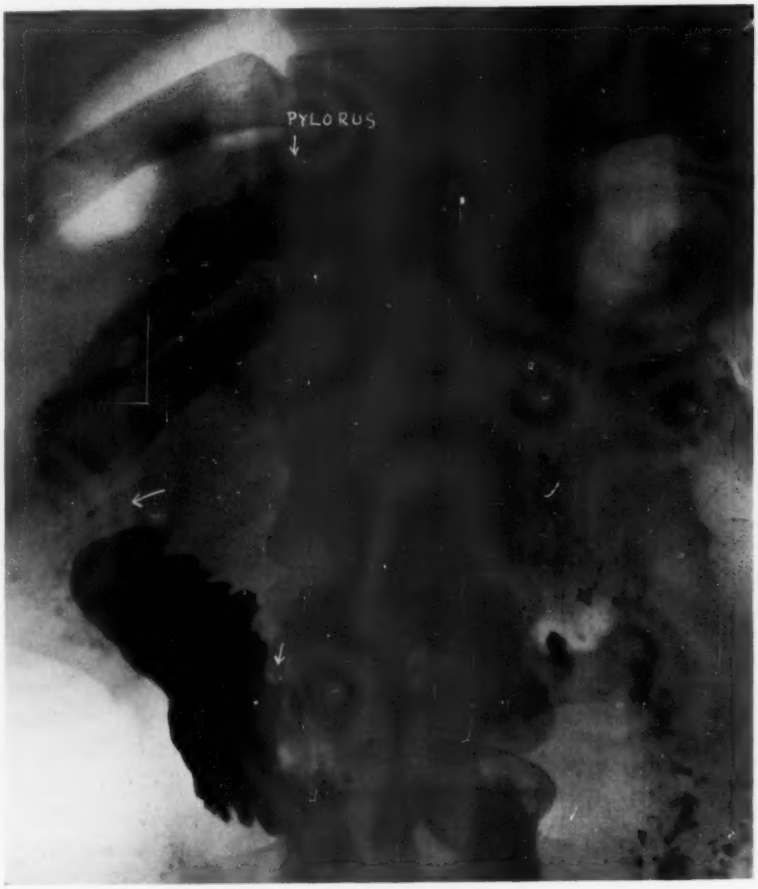


FIG. 3.—Pipe-shaped deformity of cap due to chronic ulcer (confirmed). Stasis in dependent duodenum with permanence of valleculae conniventes (arrows). No obstruction of the third and fourth portions of the duodenum was found at operation.

there was no peristalsis in any part of the duodenum beyond the cap. When the patient was lying on her left side, the barium easily entered into the jejunum. At operation, the diagnosis was confirmed and no obstruction was found. This observation does not conform to the statement that mega-duodenum occurs in hyposthenic persons; that the cap is involved in the dilatation; and that the mucosal pattern is normal.[18]

(6) *Duodenal Stasis in Diseases of Other Organs.*—In over 2,000 examinations reviewed, duodenal stasis was recorded in the following instances:

Jejunitis, two cases; jejunal ulcer after gastro-enterostomy without obstruction of the afferent loop, one; cancer of prepyloric region with permanent patency of the pylorus, two; starvation with rapid gastric evacuation and permanent patency of the pylorus, two; gastritis with hypersecretion, three; biliary colic during examination, one case. In the cases of permanent patency of the pylorus, the entire duodenum was continuously overflooded with barium; in those with gastritis, the passage through the duodenal cap was accelerated; but in the cases with jejunitis and jejunal ulcer and in the case with biliary colic, neither of these mechanisms was observed. In active

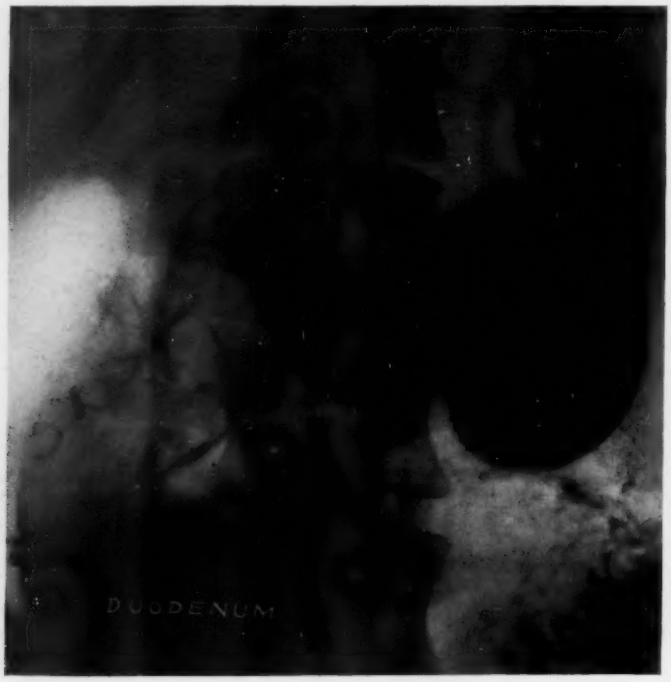


FIG. 4.—Duodenal stasis in active ulcer of posterior wall of cap.

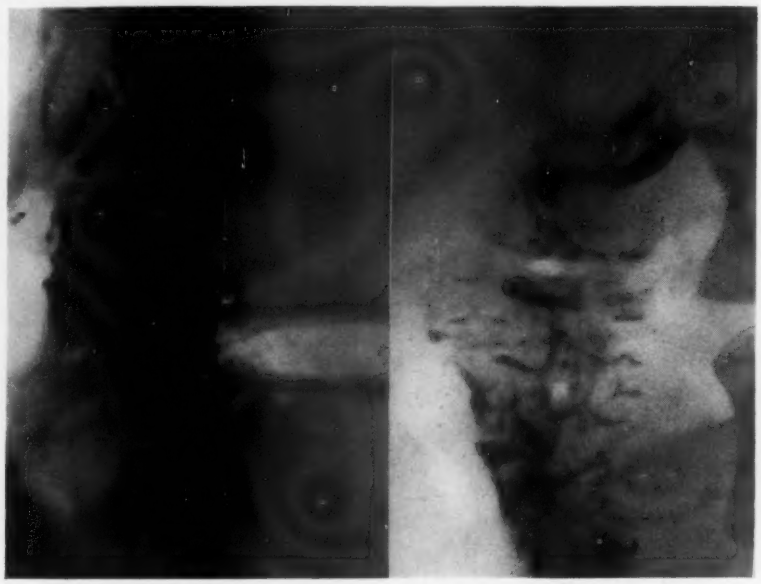
duodenal ulcer, duodenal stasis is inconstant. Statistical data would not reveal the real relation, for the development of duodenal stasis in these cases depends upon a variety of interrelated functional disorders rather than on the size or localization of an ulcer. In duodenal ulcer, stasis seems to occur more commonly when there is no pylorospasm.

(7) *Acute Angulation of the Duodenojejunal Flexure.*—Among 100 cases selected at random, an especially acute angle of the duodenojejunal flexure was found in 18 instances; there was no stasis.

(8) *Duodenal Stasis in Intestinal Atony.*—Two cases were observed in which duodenal stasis alternated with atony of the upper small intestines. These patients had vague abdominal symptoms; the clinical findings were not significant. The condition observed suggests some type of disordered nervous control.

Experimental Findings.—Experiments were made with the object of studying: (1) The interrelations between duodenal stasis and the rate of passage through pylorus and cap both in normal and pathologic conditions; (2) the possible production of duodenal stasis by abdominal pain.

(1) A. Three men with apparently normal stomachs and duodenums were given 200 cc. of the usual barium sulphate suspension. Gastric and duodenal evacuation was found to be normal. After ten minutes, each was given the yolks of three eggs. In one person, this had no effect upon the passage through stomach and duodenum; but in the duodenal mucosa transverse rugae appeared in which the barium seemed to be "caught" (Fig. 5). In the two other persons, the pylorus closed a few minutes after ingestion of



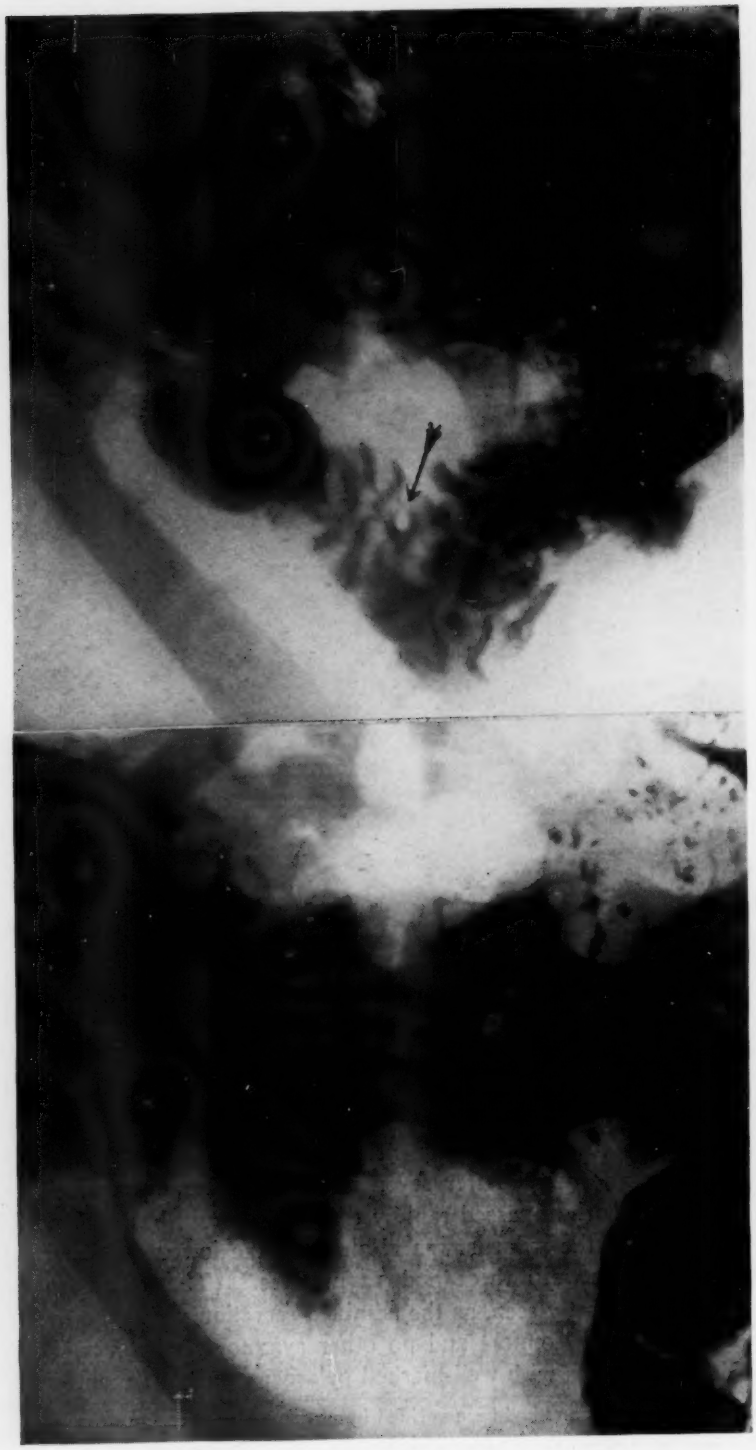
A B

FIG. 5.—Mucosal relief. (A) After ingestion of plain barium suspension. (B) Twelve minutes after additional ingestion of eggyolks; the opaque mixture is "caught" in transversal rugae which have formed in the meanwhile.

the eggyolks; the stomach enlarged slightly by loss of tone, and gastric peristalsis slowed down. No opaque medium having been seen passing through the pylorus during the subsequent 25 minutes, 1/50 grain of atropine was injected subcutaneously. After seven and 12 minutes, respectively, the pylorus relaxed, the barium passed rapidly through the cap, but each portion which passed through the pylorus was retained at the lower duodenal knee for periods varying between three and 12 minutes.* The valleculae conniventes were not distinctly seen, as the admixed secretion veiled the mucosal relief. There was no discomfort and no other symptoms whatever.

(1) B. Three patients with well-marked pylorospasm but without demon-

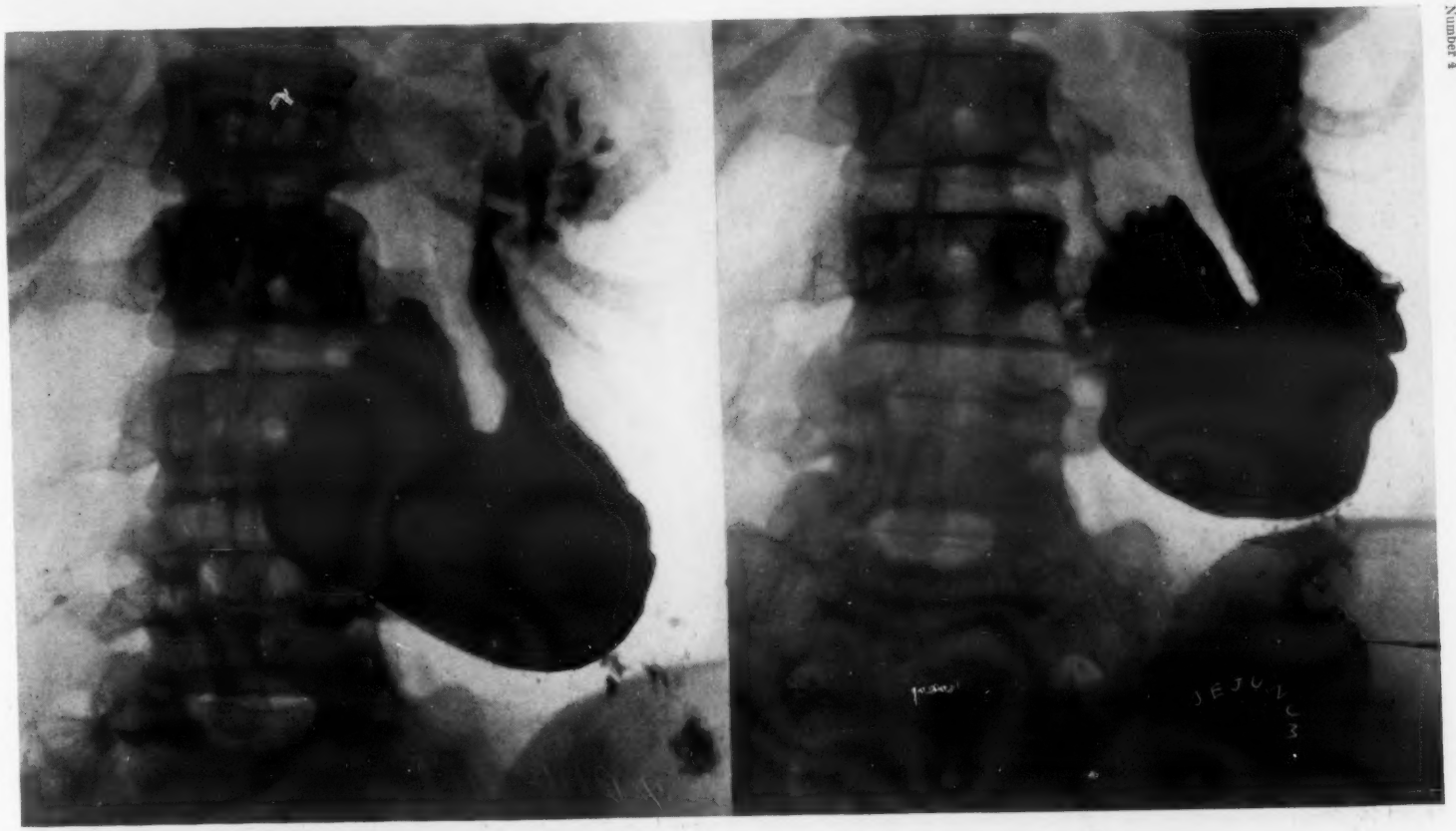
*It is known, of course, and had been verified in numerous examinations, that atropine medication does not, in itself, induce duodenal stasis.



A B

FIG. 6.—Pyloric contraction following addition of eggyolks to the opaque medium. (A) Twelve minutes after ingestion of eggs. (B) Twenty minutes later; after injection of atropine; the pylorus has relaxed; there is well marked duodenal stasis. The arrow points to the papilla of Vater.

FIG. 6.—Pyloric contraction following addition of eggyolks to the opaque medium. (A) Twelve minutes after ingestion of eggs. (B) Twenty minutes later, after injection of atropine; the pylorus has relaxed; there is well marked duodenal stasis. The arrow points to the papilla of Vater.



A B

FIG. 7.—(A) Twenty minutes after ingestion of barium; severe pylorospasm. (B) Three hours later; pylorospasm still present although some barium has passed on into the jejunum. Note entire absence of any barium in the duodenum.

FIG. 8.—Same case as shown in Figure 7. (A) Twenty-five minutes after injection of atropine; pylorus open, stasis in dependent duodenum. (B) Three hours later; stomach almost empty, pronounced duodenal stasis.

strable lesion of stomach and duodenum were examined before and after atropine medication. The first, a young woman with amebic colitis, showed marked gastric hypersecretion and pylorospasm lasting for more than three hours; no barium could be pressed through the pylorus. Thin streaks of barium, not visible on fluoroscopy, were discovered on roentgenograms on which they were found spread over various intestinal loops at four hours; but during this time, the duodenum was passed so rapidly that neither the cap nor the distal parts could be seen. The following day, examination was

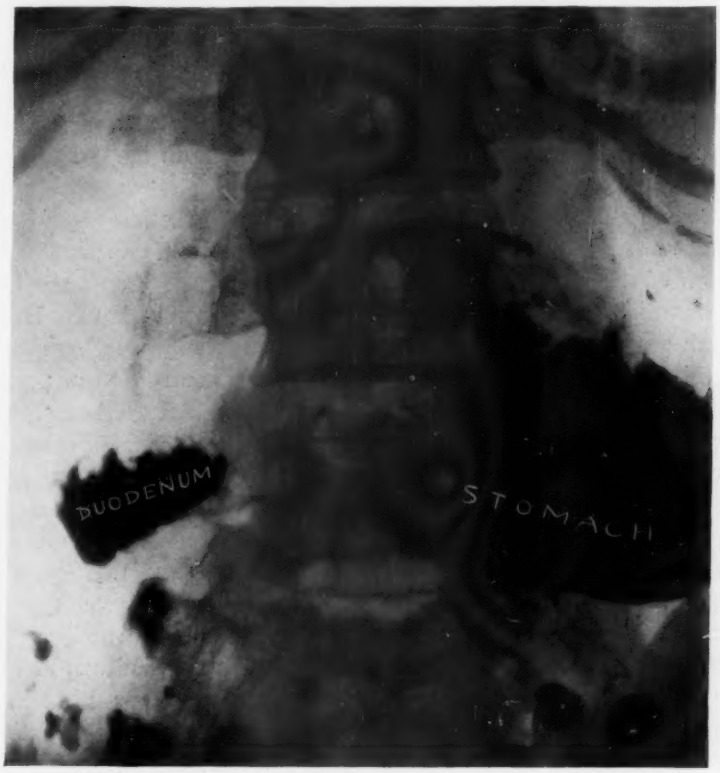


FIG. 9.—Same case as shown in Figures 7 and 8. Three and one-half hours after injection of smaller dose of atropine: Pylorospasm, slight duodenal stasis. The series illustrated in Figures 7, 8, and 9 shows the experimental production of duodenal stasis with almost quantitative pharmacologic results.

repeated after hypodermic injections of atropine, 1/50 grain 12 hours before examination, and another 1/50 grain 20 minutes before it. The pylorus then opened a few minutes after barium had been given by mouth; barium passed so rapidly through the cap that the latter could not be seen distinctly; it then accumulated in the dependent duodenum where it was retained during the subsequent four hours (Fig. 8). The patient stated that she felt no discomfort whatever. After two days, examination was repeated without atropine medication, and the findings were identical in every respect with those observed the first day. Again, 48 hours later, only 1/100 grain of

atropine was injected 20 minutes before examination; pylorospasm was less marked, some barium passed through the duodenum, and slight retention occurred at the lower duodenal knee (Fig. 9). In the second patient, severe pylorospasm having been found on a routine examination, injection of 1/100 grain of atropine resulted in normal gastric evacuation with arrest of the barium at the tip of the cap; there was no duodenal stasis. A second injection of 1/100 grain, made 35 minutes later, induced definite retention in the dependent duodenum, the barium passing through the cap without arrest at its tip. There were no symptoms. In a third patient, examination was made, first, without atropine; then, 50 minutes later, after injection of 1/100 grain; and finally, after 24 hours, after injection of 1/50 grain. There was pylorospasm on the first examination; normal passage through the cap with arrest at its tip on the second one; and very rapid passage through pylorus and cap with slight retention in the dependent duodenum on the last examination, in the entire absence of any symptoms.

(2) As previously reported,[16] transient atony of the intestines may result from abdominal colic, both spontaneously or artificially produced, *e.g.*, by distention of the renal pelves. In two patients of this group, the left renal pelvis was distended by retrograde pyelography, barium having been given by mouth 20 minutes before. There was severe colicky pain, complete atony of the colon and upper small intestines, and tonic contraction of pylorus and in ileal loops, lasting in both cases for more than seven hours. In both instances, the dependent duodenum was widened during this period, and the opaque medium was retained in it for about three hours. Both one day before and one day after the experiment, the entire digestive tract was normal in the two patients. Widening and atony of the duodenum were also seen in one case of biliary colic, as above described (Fig. 1C).

Discussion.—In the series here reported, duodenal stasis with well-marked retention was comparatively rare in anatomic obstructions, but more common as a result of, what appears to be, a reflex mechanism. The observations would seem to indicate that duodenal stasis occurs: First, when the passage through pylorus and cap is accelerated; and secondly, when there is a lesion in the jejunum. Normally, two valves, the pylorus and the tip of the duodenal cap, control the flow from the gastric reservoir into the small intestines. When their action is impaired either anatomically or, *e.g.*, by atropine medication, the dependent duodenum may in some instances act as a third potential valve which delays the passage into the jejunum. As a potential mechanism, this is not constant. As far as we know, this valve is not a preformed sphincter; but, by atony, as well as by a tonic contraction in the horizontal portion, a retardation of the flow occurs, which seems to make up for accelerated passage through pylorus and upper duodenum.

The compensatory action of potential valves is nothing unusual in the physiology of the digestive tract in man. For instance, when the hepatic flexure is smoothly rounded, the cecocolonic sphincter is frequently well developed or contracted; and, vice versa, when the hepatic flexure is kinked, the

sphincter may not be seen distinctly. Similarly, retention in cephalad parts is known to occur when distal segments are diseased, *e.g.*, that pylorospasm occurs in lesions of the ileum, cecum, and colon. It may be that this type of retention represents a kind of protective mechanism which prevents flooding of irritated loops.

In this series, duodenal stasis was unexpectedly found to be rare in instances of anatomic compression and in kinking of the duodenum. This is at variance with other reports on the subject, but is in accord with observations on obstruction in other parts of the intestines. It is well known that sharp kinks, and unusual positions, rarely impair normal function,[2, 3] and that there has to be a considerable amount of compression or stenosis before dilatation and retention become definite. On the other hand, spasms and atony often interfere distinctly with the passage. Ileal stasis, for instance, a condition much discussed in the past, is decidedly rare in the presence of extensive perityphlitic adhesions, and even more so in obstructive tumors of the cecum; but it is less uncommon in inflammatory conditions not associated with stenosis, where it seems to be due to reflectoric inhibition of the passage. It is not here denied that acute obstruction of the duodenum by a mesenteric vessel may occur; but the question is raised whether the diagnosis of chronic, recurrent, or intermittent arteriomesenteric occlusion is built on firm ground. As above mentioned, the conventional roentgenologic signs of duodenal obstruction are indirect and ambiguous. But the clinical signs are not characteristic either—vomiting relieved in the genupectoral position, one of the cardinal symptoms, has been found by us in verified cases of hydrops of the gallbladder, acute pancreatitis, duodenal ulcer, renal calculi—in all of which cases it did not recur after surgical treatment of the underlying lesion. It is difficult to see why migraine, another disorder ascribed to duodenal stasis, should be the result of arteriomesenteric occlusion when it occurs in hyposthenic women over 30 years of age,[18] while it is admittedly independent of it in stout persons; moreover, in migraine neither vomiting nor the "toxic" symptoms are relieved by or in the genupectoral position. In extensive studies on the relation of migraine to various extrinsic factors, the author has hitherto failed to see a patient in whom duodenal stasis was present during the attack.

The third part of the duodenum is quite movable and slides back easily in the supine position; pressure upon it by the spine is very common during examinations in recumbency; but in no instance have clinical symptoms been observed by us under these conditions, even when the pressure by the spine caused well-marked delay of the passage. Anatomically, nothing is known about the spatial relation between the mesenteric arteries, aorta, and duodenum in healthy persons of the hyposthenic type during operation—that is, under the influence of anesthetics, operative shock, and opening of the abdominal cavity; factors known to profoundly affect the position and shape of the intestinal organs. Therefore, in regard to the angle formed by a movable vessel and its influence upon a hidden intestinal loop difficult to approach,

it seems somewhat doubtful whether operative findings, that is, observations made under quite unphysiologic conditions, can be accepted as conclusive proof. One may ask whether the conception of arteriomesenteric occlusion is not an example of what Barclay has called the persistent attempt to make the viscera conform to the pattern of the dead. One may also ask whether perhaps this occlusion is not another "Lane's kink," that is, an abnormality not verifiable by the most experienced observers.[2] Many of these alleged anomalies are, in reality, normal conditions; Barclay has conclusively shown that they often represent individual variations; and the author has previously pointed out that they may also correspond to physiologic changes occurring during digestion.[3, 16] These two views are complementary; in the matter here discussed, both methods of approach demonstrate that duodenal stasis may be unnoticed by the person in whom it is observed: hence, that it is not synonymous with disease.

We are, therefore, forced to the conclusion that the roentgenologic demonstration of duodenal stasis is not, in itself, sufficient to warrant the diagnosis of obstruction, since the finding does not even prove that the clinical symptoms are due to duodenal stasis. In a majority of cases, duodenal stasis is a compensatory mechanism, not characteristic of any particular disease. From this reflectoric condition, anatomic obstruction is to be distinguished by the presence of the "direct" roentgenologic signs of stenosis or compression.*

SUMMARY

(1) In this series, duodenal stasis was found to be rare in anatomic obstructions: such as compression by extrinsic tumors, fixation by adhesions, kinking, and intrinsic growth. Excessive stasis was present in one case of megaduodenum.

(2) Both in physiologic and in pathologic acceleration of the passage through the pylorus and duodenal cap, duodenal stasis is common. In the presence of pylorospasm and of physiologic pyloric contraction, duodenal stasis could be produced by atropine medication, if this caused the pylorus to relax. Abdominal colic, spontaneous or experimentally induced, may also cause duodenal stasis.

(3) Observations on jejunitis and on permanent patency of the pylorus, and experiments in man, suggest that duodenal stasis may occur as a compensatory or as a "protective" mechanism when the food passes through the proximal duodenum too rapidly.

(4) The pathogenesis and incidence of arteriomesenteric occlusion are questioned.

(5) Duodenal stasis was observed to occur in the entire absence of clinical symptoms. Clinical symptoms, allegedly typical of duodenal stasis, were found in diseases of an entirely different nature. Hence the presence of

* Duodenal stasis due to anatomic obstruction will be discussed in a separate report (in collaboration with P. F. Sahyun).

duodenal stasis, as demonstrated roentgenologically, neither indicates anatomic obstruction, nor proves that the clinical symptoms are due to duodenal stasis.

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MORBIDITY FOLLOWING CHOLECYSTECTOMY

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THIS COMMUNICATION records a critical analysis of patients returning to the Follow-Up Clinic of the Hospital of the University of Pennsylvania, from one to four years after cholecystectomy, with symptoms indicating that the operation had not given them the relief which either they or their surgeon anticipated. The cases were selected from a larger series, of 504 patients with gallbladder disease, operated upon on the service of Dr. E. L. Eliason, during the 12 years from 1922 to 1934. Various aspects of this complete series, including mortality, type of pathology encountered, and operative technic, have recently been reported by Eliason and Erb.[2] The present discussion is not concerned with such factors as these, nor with anatomic defects, such as postoperative hernia, wound infection or fistula, but only with unsatisfactory functional end-results. Moreover, since the inadequacy of cholecystostomy as compared with cholecystectomy is well recognized, we will confine ourselves to the results after the latter procedure.

There are available for review, 264 instances of cholecystectomy, whose records include follow-up notes extending over a period of at least one year, a follow-up percentage of 85 of all cholecystectomies performed during this period. Two hundred thirty-six of these patients, or 89 per cent, have reported themselves in good health and relieved of all symptoms. In the records of the remaining 28, mention is made of one or more residual symptoms. In seven instances, these symptoms were found on investigation to be due to causes extraneous to the biliary tract and for the most part developing after the operation. These patients were entirely free of symptoms related to the gallbladder or ducts and will be discussed as Group IV. In five patients, notes made soon after operation indicate persistence of biliary symptoms, but later the patients in this group (Group III) obtained complete relief. There are left 16 patients with residual trouble of one form or another, definitely attributable to the biliary system, or attributed to this system correctly or incorrectly at the time operation was determined upon. To put the matter in another way, this analysis shows that cholecystectomy gave ultimate relief to 94 per cent.

The 16 unrelieved patients may be subdivided into two groups. Group I are those in whom no significant biliary lesion was found at operation. The preoperative diagnosis was, therefore, incorrect. Group II consists of those who, at operation, had definite lesions of the gallbladder or its ducts but whose symptoms persisted despite the removal of the gallbladder. In most instances, these patients gave atypical histories of gallbladder disease or re-

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ported symptoms additional to those which could be related to the biliary tract. The diagnosis of gallbladder disease in these instances, therefore, only partially explained the patients' symptomatology, and this diagnosis can be described as incomplete. A careful analysis of these cases of an incorrect or incomplete preoperative diagnosis brings to light some interesting features.

Although the ratio of males to females in the entire series of biliary operations reported by Eliason and Erb[2] is approximately one in six, there was only one male in this group of 16 poor results. This emphasizes the difficulty of differential diagnosis of abdominal conditions in women. It also seems noteworthy that prior to their cholecystectomy six, or 40 per cent, of the women had had a previous pelvic operation with removal of one or both tubes and ovaries. In reviewing these records, it seems probable that the symptoms of artificial menopause complicated and confused the diagnosis of gallbladder disease.

In dealing with conditions in which the history given by the patient plays a major rôle in diagnosis, a clear understanding between the patient and the historian is of paramount importance. Frequently, errors are traceable to the fact that the patient does not comprehend our questions or else we do not understand his replies. The historian may ask leading questions and a frightened patient obligingly supplies false information. The intelligence quotient of the patient may make accurate history taking impossible or language difficulties may exist, in which case an interpreter may further complicate the situation. We have no means of assessing the part played by the first two factors in our own diagnostic errors, but it was not surprising to find that in five instances the history states that "the patient understands and speaks English very poorly." No doubt, similar but unrecorded misunderstandings arose in other cases. Often, in patients whose histories are unreliable or atypical, laboratory data have had too great an influence upon the diagnosis. For example, cholecystography is reliably accurate in determining the function of the gallbladder at the moment, so that, barring technical errors in the administration of the dye, a roentgenographic report of nonfunctioning gallbladder means exactly that. Yet that is far from implying that the impaired function of this single organ necessarily accounts for all the symptoms suffered by the individual. Every pathologist can testify that many of us live and die peacefully ignorant of the fact that our stone-laden gallbladders have neither concentrated nor emptied for years.

Incorrect Diagnoses.—Group I: There were eight patients in whom an incorrect diagnosis of gallbladder disease was made preoperatively. Each had had adequate preoperative studies, many being investigated exhaustively on the medical service before they were transferred for surgery. In a fair number, an honest doubt as to the diagnosis was expressed at the completion of study. Nevertheless, they were operated upon with the suspicion of gallbladder disease, and cholecystectomy performed, although the surgeon could not identify gross evidence of biliary disease. Hence, they must be classed as diagnostic errors. In most instances the actual cause of the symptoms was disclosed at operation. In some, it was not evident at this time but was

made manifest or inferred from later developments. It is obvious that this small group does not include all the cases in which we committed errors of diagnosis in gallbladder disease, but only those in which cholecystectomy was performed and the results were unsatisfactory. There were other cases, of course, in which the operator left the gallbladder intact or simply drained it when his preoperative diagnosis was found to be in error. In the light of later developments, the sources of error often stood out strikingly and symptoms which were passed over as unimportant took on a new significance. Such was the case in a patient (Case 1) who two years after cholecystectomy was found to have a huge carcinoma of the greater curvature of the stomach. The same is true of the one diagnosed pylorospasm (Case 2). At operation both stomach and duodenum were inspected and palpated but the negative roentgenologic studies of the gastro-intestinal tract doubtless deterred the surgeon from opening the stomach. Had this been done, an ulcer on the posterior wall might have been found. A case designated as perihepatitis (Case 3) is of more than usual interest. Fitz-Hugh[3] has described this condition, and attributed it to gonococcal infection originating in the pelvic organs. In this patient there was an acute serositis of the hepatic capsule and adjoining parietal peritoneum, with filmy adhesions. The clinical picture was that of acute cholecystitis. Another case, studied on the Neurologic Service, presented many symptoms which could be interpreted as fairly typical of gallbladder disease. At that time we were unfamiliar with the clinical picture of hyperinsulinism resulting from a pancreatic adenoma. It is interesting to speculate upon whether the "fits," for which she was admitted to the hospital, were due to this cause. The question cannot be answered since no blood sugar determinations were made and the patient cannot be traced. A functional digestive disorder seems a reasonable diagnosis in this patient as well as in one other in the series (Cases 4 and 5). Three diagnoses were corrected to adhesions, in two instances postoperative and in the third congenital (Cases 6, 7 and 8). The diagnosis of gallbladder disease, in each case, was made with reservations because of the history. None benefited from cholecystectomy, and improvement was hardly to be expected, inasmuch as the principal lesion lay outside the gallbladder. It will be noted that several of these patients had stones, pericholecystic adhesions or other evidence of cholecystic disease, so to that extent the diagnosis was correct. Brief abstracts of the records of these eight cases follow.

BRIEF ABSTRACTS OF EIGHT CASES WITH INCORRECT PREOPERATIVE DIAGNOSES

Group I

Cases with No Significant Gallbladder Lesions

Case 1.—*Gastric Carcinoma:* Female, age 54.

History.—Nausea, vomiting and gaseous distention—four years. Hunger pains two to three hours after meals. Two attacks of right upper quadrant pain with some jaundice; none of this pain recently. Weight loss of 50 pounds in year. Cholecystogram—nonfunctioning gallbladder.

Operation.—Single stone at ampulla. Chronic thickening of gallbladder wall. No stones felt in common duct. No note about stomach or duodenum.

Result.—Continued pain; gaseous distention and occasional diarrhea. Lost more weight. After 21 months, a large carcinoma of greater curvature of stomach was found during course of pelvic operation. (Note early symptoms overlooked.)

Case 2.—*Pylorospasm:* Female, age 32.

History.—Recurrent epigastric pain—five years—food relief. Nausea. Flatulence. Loss of 20 pounds in five months. Anorexia. Gastro-intestinal series negative.

Operation.—Hypertrophy and spasm at pylorus; no ulcer found. Adhesions around gallbladder. No stones.

Result.—Burning in epigastrium returned four months after operation. After two years, advised admission to Medical Ward with diagnosis of peptic ulcer, but patient went elsewhere.

Case 3.—*Perihepatitis:* Female, age 26.

History.—Pain in right upper quadrant, six days—worse on deep breathing. Nausea and vomiting. Local tenderness and rigidity.

Operation.—Perihepatitis—acute, possible gonococcal origin (previous operation for tubal disease). No biliary lesion.

Result.—Two years—persistent gaseous indigestion.

Case 4.—*Functional Neurosis:* Female, age 45.

History.—Admitted to Neurologic Service because of so-called "fits." Multiple complaints, including gaseous dyspepsia and jaundice; from which history of gallbladder dyspepsia could be inferred. During "fit," local signs suggested cholecystitis. Cholecystogram—nonfunctioning gallbladder. Medical consultant doubtful about organic disease.

Operation.—Fatty infiltration of gallbladder, and enlarged lymph node near cystic duct. No stones.

Result.—Improved, but still has epigastric distress. (Question of pancreatic adenoma.)

Case 5.—*Functional Neurosis:* Female, age 38.

History.—Nausea, vomiting and diarrhea for 20 years. Studied, Discharged. Returned two years later, with story of pain in right upper quadrant and reported transient jaundice. Gastro-intestinal series negative.

Operation.—Possible kinking of cystic duct, and slight thickening of gallbladder wall. No stones.

Result.—During following two years, two readmissions for vomiting, which was never verified.

Case 6.—*Postoperative Adhesions:* Female, age 44.

History.—1905, indigestion began following pregnancy. 1915, pelvic operation. 1925, cholecystectomy performed in another hospital for colic and jaundice. Three later admissions to same hospital—diagnosed adhesions. 1932, admitted with history of pain in scapular region, nausea, chills but no jaundice. Roentgenogram indicated adhesions. Operated upon, because of suspicion of common duct stone.

Operation.—Extensive adhesions, some of which thought to cause kinking of common duct. Latter explored. No stones or obstruction.

Result.—During next two years, recurrent attacks of pain with nausea.

Case 7.—*Adhesions—Duodenal Ileus:* Female, age 46.

History.—Typical history of colic, indigestion but no jaundice—two years. Vomiting with relief.

Operation.—Adhesive bands making traction on cystic duct, and involving also duodenum and colon. No stones.

Result.—Relief for one month. Symptoms returned. Gastro-intestinal series showed duodenal stasis. Reoperated upon, and duodenojejunostomy performed. Relieved for 15 months, when pain returned. Reoperated upon, and adhesions freed. Four months later, same incapacitating pain.

Case 8.—*Postoperative Adhesions:* Female, age 32.

History.—Nausea, belching and constipation since childhood. Appendicectomy, and subsequent operation for intestinal obstruction due to adhesions. Recent attacks of severe

right upper quadrant pain, referred to shoulder. Cholecystogram—normal function. Gastro-intestinal series—irregularity in pyloric region suggesting prolapse of mucosa.

Operation.—Extensive adhesions. Stomach and duodenum normal. Cholesterosis of gallbladder.

Result.—Continued upper abdominal pain for two years, with eventual reoperation elsewhere, for intestinal obstruction.

Incomplete Diagnoses.—Group II: A second group of eight patients consisted of those in whom, as has been stated, the diagnosis was partially correct, in that a definite cholecystic lesion was found at operation. Correction of the local condition by cholecystectomy, however, failed to relieve all the symptoms, and the latter may be attributed to the presence of "silent stone," the existence of which was disclosed only by roentgenologic examination. It is significant that in each case the biliary symptomatology was complicated by other complaints. Usually, thorough investigation, or the developments of time, threw light upon the real sources of distress in these patients. In three instances, we remain uncertain concerning the cause of their complaints. It may be suspected at first glance that this group contained patients in whom common duct stones were overlooked at the time of cholecystectomy. This has been emphasized by numerous authors, including Cattell,[1] in their analyses of cholecystectomy failures. None of these cases of ours had jaundice, chills, fever or other manifestations of common duct obstruction. So far as we are able to ascertain, none of these unsatisfactory results were due to undiscovered stones in the ducts, although we have operated upon such patients who have had a cholecystectomy elsewhere, and some of ours may have gone to other surgeons rather than return to our Follow-Up Clinic. The common duct was explored in 18 per cent of the total number of operations for inflammatory disease of the gallbladder. In about one-third of these, the gallbladder was emptied and drained instead of being removed. This was sometimes done deliberately in cases in which the operator felt that possible undiscovered stones remained in the ducts. The presence of the gallbladder provides a valuable anatomic landmark in the event of secondary explorations of the ducts. Common duct stricture due to operative trauma occurred in one case not included in this discussion, owing to the fact that following early reoperation, a perfect functional result was secured. Although seven of the eight cases in this group had cholelithiasis, this does not invalidate the accepted contention that the best results of cholecystectomy occur in calculous rather than in noncalculous gallbladders. It merely emphasizes the fact that the presence of stones in the gallbladder or even in the ducts does not of necessity mean that the patient will have symptoms therefrom. Actually, only 15 per cent of the cholecystectomies included in this series were performed for chronic, noncalculous cholecystitis. Cholecystostomy was frequently performed in the noncalculous cases, when the operator was doubtful whether the gross signs justified cholecystectomy. Attention is called to the atypical history in each case in the appended abstracts (Group II). Two patients suspected of peptic ulcer are perhaps noteworthy. In one (Case 2), this was the preoperative diagnosis. At operation, the surgeon, after search-

ing in vain for ulcer, removed the gallbladder. The residual symptoms suggest that symptoms were due to the phrenospasm and duodenal stasis apparent on roentgenologic examination. In the second (Case 5), ulcer was suspected from the roentgenologic evidence of deformity of the duodenal cap. Pericholecystic adhesions found at operation seemed to account adequately for this defect. Unfortunately, no note was made concerning inspection or palpation of the duodenum, so we are left uncertain as to the correct explanation of the case. The recorded postoperative complaints, it must be admitted, were not typical of ulcer in this case.

BRIEF ABSTRACTS OF EIGHT CASES WITH INCOMPLETE DIAGNOSES

Group II

Cases With Definite Lesions of the Gallbladder, in Which Symptoms Persisted

Case 1.—Female, age 32.

History.—Atypical history of pain in left hypochondrium, eructations, fulness after meals, headache and constipation.

Operation.—Single stone. Adhesions about appendix; removed with gallbladder.

Result.—Same symptoms as before operation. Colon responsible?

Case 2.—Female, age 54.

History.—Burning epigastric pain—one year—usually a few hours after eating, and always relieved by soda. Gastro-intestinal series showed phrenospasm and duodenal diverticulum, with stasis in second portion. Tentative diagnosis: Duodenal ulcer.

Operation.—Inspection and palpation of stomach and duodenum revealed no ulcer. Gallbladder wall thickened, and stone impacted in cystic duct.

Result.—During following two and one-half years, continuous gaseous indigestion—sour regurgitations, distress after fatty foods.

Conclusion.—No relief from operation due to concomitant duodenal disorder.

Case 3.—Female, age 48.

History.—Bilateral salpingo-oophorectomy for a Sampson's cyst, eight years before. Indigestion with severe right upper quadrant pain—two years. Epigastric hernia found, relief secured from belt. Recently, constant discomfort in upper abdomen relieved by soda. Some tenderness over gallbladder. Operation undertaken as diagnostic procedure. Diagnosis: Gallbladder disease or colonic adhesions. Marked cancerphobia.

Operation.—Gallbladder gray and thickened. Common duct, not dilated.

Result.—During next year, continued distress—complete investigation. Diagnosis: Anxiety neurosis and endocrine dysfunction.

Case 4.—Female, age 49.

History.—Typical, with many additional symptoms, including hunger pains relieved by food and generalized neuralgias.

Operation.—Single stone. Adhesions about gallbladder. Cirrhosis of liver.

Result.—None of previous colic, but all other symptoms persistent over three-year period. Hepatic disease?

Case 5.—Male, age 29.

History.—Typical indigestion, without colic—three years. Cholecystogram—nonfunctioning gallbladder. Gastro-intestinal series showed duodenal defect, probably due to adhesions but possibly an ulcer.

Operation.—Adhesions to gallbladder. Stones. No note about duodenum.

Result.—Not relieved after 18 months. Symptoms may be due to ulcer in addition to biliary lesion.

Case 6.—Female, age 53.

History.—Atypical. Pain chiefly in left upper quadrant and referred to scapulae—indi-

gestion. Linguistic difficulties. Gallbladder palpable. Cholecystogram—nonfunctioning gallbladder. Laboratory evidence of slight icterus.

Operation.—Many stones.

Result.—Two years, complains of same symptoms but especially pain in left side. Etiology unknown. Silent stones.

Case 7.—Female, age 30.

History.—Adhesions about gallbladder. Stones palpated during pelvic operation. Later had colic referred to back and shoulder, vomiting and diarrhea.

Operation.—Thickened gallbladder, with stones and adhesions. One stone in cystic duct.

Result.—Symptoms, similar to those above, together with intractable constipation and backache. Functional disturbance of colon?

Case 8.—Female, age 36.

History.—Linguistic difficulties. Epigastric pain—nausea—belching. Questionable diagnosis. Cholecystogram—no function of gallbladder. Gastro-intestinal series—probably adhesions about duodenum cap. Cholesterol crystals in duodenal drainage. Cystoscopic examination negative.

Operation.—Many stones.

Result.—Seven months, same symptoms persist. Definite postoperative cystitis. Silent stones with additional obscure factors.

Delayed Relief from Operation.—Group III: We have designated as Group III, five patients who had, for from six to 16 months, symptoms similar to those which preceded operation. Eventually, they became well, and were considered as satisfactory results. We have usually attributed this delay in relief from cholecystectomy to the fact that time is required for the ducts to dilate, so that they may assume, in a measure, the function of the absent gallbladder. We had thought this delay was particularly apt to occur in young patients, or in those with biliary duct obstruction of brief duration, and have made a point of warning such patients that they must not expect immediate cessation of all indigestion. This particular group does not bear out these particular impressions.

BRIEF ABSTRACTS OF FOUR CASES WITH DELAYED RELIEF FOLLOWING OPERATION

Group III

Cases with Delayed Relief Following Operation

Case 1.—Age 25. Typical history—six years. Aerophagia. No calculi. Well, after nine months.

Case 2.—Age 54. Typical history with colic—three years—and jaundice. Stones and adhesions. Persistent indigestion, first 16 months.

Case 3.—Age 38. Atypical history—several years with pain and distention. Stones and adhesions. Several attacks of severe pain, first year. None thereafter.

Case 4.—Age 53. Typical history—seven years. Stones and adhesions. Distress after eating, first six months. Well thereafter.

Extraneous Complications.—Group IV: Our follow-up records were confused, at first inspection, by a number of patients who appeared to have residual troubles after operation. Careful analysis revealed that their symptoms were not biliary in origin, and we have designated this group of patients as Group IV. They were, in reality, relieved by the operation of all symp-

toms related to the gallbladder and their complaints, with two exceptions, arose after operation. In these two instances a second condition—hyperthyroidism and myocardial disease—was clearly recognized before operation, but cholecystectomy was considered advisable, as it might benefit the concomitant condition. Under such circumstances, we have not designated these as diagnostic errors. Appended is a list of the sources of their symptomatology.

Group IV—Extraneous Conditions

(1) Ureteral colic—right-sided.
(2) Ulcerative colitis, with epigastric pain.
(3) Pulmonary and intestinal tuberculosis, with dyspepsia.
(4) Tabes dorsalis, with epigastric pain.
(5) Subacromial bursitis—right shoulder pain.
(6) Hyperthyroidism, recognized before gallbladder operation, and not relieved by thyroidectomy.
(7) Myocardial disease, with fibrillation present before operation and persisting.

CONCLUSIONS

A study of a series of 264 cases, in which cholecystectomy was performed, with a preoperative diagnosis of cholecystitis, shows that only 6 per cent were not relieved of the symptoms for which operation was performed. In a small number this relief was delayed, and in others extraneous factors developed after operation which were attributed, incorrectly by the patient, to the gallbladder. The 6 per cent who continued with many of the same symptoms after removal of their gallbladders fall into two equal groups. In one, no gross evidence of gallbladder disease was evident at the time of operation, and cholecystectomy could not be expected to afford relief. In the other, the surgeon found a diseased gallbladder, and usually gallstones, yet the patient was not helped by cholecystectomy. In this latter group, the chief source of the patient's complaints was extrabiliary and the finding of a biliary lesion purely incidental. A certain number of these diagnostic errors were inevitable, despite thorough preoperative study of the cases. In others, the errors might have been avoided by attaching due significance to symptoms which were regarded simply as atypical; by more careful attention to the patients' own description of their symptoms; and by a recognition of the fact that, even when gallstones are actually demonstrated, it may not be fair to attribute thereto all the patients' digestive symptoms, since many gallstones are "silent" ones.

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PROTHROMBIN DEFICIENCY AND THE EFFECTS OF VITAMIN K IN OBSTRUCTIVE JAUNDICE AND BILIARY FISTULA

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WHEN Dam,[1] in 1935, showed that the lack of a fat-soluble substance which he called vitamin K (koagulations vitamin) in the diet of chicks led to fatal bleeding, he opened a new approach to the study of pathologic bleeding. Investigation of a hemorrhagic disease of cattle resulting from eating spoiled sweet clover had led to demonstration of low plasma prothrombin as the etiologic factor, presumably due to toxic effect on the liver.[2] Improvements in methods of determining plasma prothrombin[3, 4] were followed by observation of low plasma prothrombin in animals with experimental liver poisoning and biliary obstruction, in chicks with hemorrhagic disease from vitamin K deficiency, and in patients with obstructive jaundice.[3, 5, 6, 7]

Another link in the chain was supplied by the experimental proof that fat-soluble vitamins are not absorbed from the intestine in the absence of bile salts.[8] Practical application of these facts has led to successful treatment of prothrombin deficiency in patients with liver disease by means of extracts containing vitamin K.[9, 10] Considerable progress has been made in the purification of vitamin K, though a preparation suitable for parenteral use is not yet available. Much study has been given to developing better methods of assaying the vitamin K content of various animal and vegetable fats, but a method based on the protective or curative effect on chicks must still be used.[11]

Data included in the present communication were obtained in the study and treatment of patients with obstructive jaundice or biliary fistula on the Surgical Services of the Massachusetts General Hospital during the past year. Although the work is now in progress, the results to date are so striking that it is felt a preliminary report is indicated.

Methods Employed.—Plasma prothrombin was determined by the method of Warner, Brinkhous and Smith,[5] with modifications. Instead of using serial dilution technic, standardized normal control plasma was titrated in exactly the same way as the unknown, both being done in triplicate. The incubation period of the mixture before adding fibrinogen was kept constant and brief. Since the final coagulation time is taken as inversely proportional to the prothrombin concentration, there results the formula, $\frac{TC}{TX} \times \frac{DC}{DX} =$ percent-

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age of normal plasma prothrombin in unknown, where TC = clotting time of control, TX = clotting time of unknown, DC = dilution factor of control and DX = dilution factor of unknown. Fresh plasma is taken from the control for each set of titrations. A group of six laboratory workers were used as controls, and little difference among them or variation from time to time was observed, so long as titration temperature was kept constant. Each new lot of reagents, however, must be standardized.

In every instance the clotting time of recalcified plasma with addition of excess of thromboplastin (beef lung extract) was determined. As a rule this gave results in relation to the normal control similar to those obtained by the method of Warner, Brinkhous and Smith. Occasionally, however, particularly in abnormal plasma, there was wide discrepancy. The results obtained with the method of recalcification of oxalated plasma to which thromboplastin has been added are not reported here.

Fibrinogen was determined in duplicate on the oxalated plasma by the method of Cullen and Van Slyke,[12] the clot obtained from 1 cc. of plasma being subjected to microdigestion and nesslerization. In several instances dilute thrombin solution was used to precipitate the fibrinogen and the results checked closely with those obtained by using calcium chloride. This was done to exclude the possibility of incomplete conversion of fibrinogen to fibrin in the presence of prothrombin deficiency.

Plasma bilirubin was measured as follows: Two cubic centimeters of plasma were combined with 1 cc. of the diazo reagent and allowed to stand ten minutes. Then 2 cc. saturated ammonium sulphate plus 10 cc. 95 per cent alcohol were added. The mixture was centrifuged, and the supernatant fluid was read against the cobaltous sulphate standard prepared according to McNee and Keefer.[13]

Various liver function tests were performed repeatedly on these patients, including the bromphalein and hippuric acid tests. These data, however, will not be discussed here.

The vitamin K extract used in this work was prepared from fresh spinach according to the method of Dam.[14] The extraction was continued through the acetone and petroleum ether refluxings, and from 50 kg. of spinach 30 Gm. of tarry liquid were obtained. The extract was thoroughly mixed with sodium taurocholate and sodium glycocholate (Merck) in the proportion of 1.0 Gm. of extract to 4.5 Gm. of each bile salt preparation, and the mixture was put up in capsules containing 0.2 Gm. each. The mixture was kept in a cold box at − 35°C., used also for preserving the solutions of fibrinogen thrombin and thromboplastin.

Usually determination of plasma prothrombin was made repeatedly before and after operation, and vitamin K-cholic acid mixture was given orally as needed. In two cases, patients T. P. H. and M. Y., the mixture was given through a jejunostomy. One patient, M. Y., was seen only after operation, when massive bleeding had set in and six transfusions had been ineffective in controlling it.

Results Obtained.—In Table I are shown data from 13 patients, 12 of whom were suffering from obstructive jaundice and varying degrees of liver damage, while one, M. Y., had a postoperative external biliary fistula. The amount of vitamin K-cholic acid mixture taken and the duration of treatment are shown, together with plasma concentrations of prothrombin and bilirubin. The average increase in plasma prothrombin under vitamin K therapy was 32.8 per cent.

TABLE I

PREOPERATIVE RESPONSE OF PLASMA PROTHROMBIN LEVEL TO VITAMIN K-CHOLIC ACID MIXTURE*

Patient	Age	Diagnosis	Jaundice, Duration, Weeks	Treatment, Duration, Days	Vitamin K Bile Salts, Total Gm.	Plasma Prothrombin Per Cent	Plasma Bilirubin Mg. Per Cent
L. H. S.	33	Common duct stone	14	4	3.2	49.8	10.1
						86.8	10.1
J. B.	47	Carcinoma of pancreas	3	5	4.0	71.4	19.2
						86.6	24.2
H. C. K.	32	Common duct stricture	4	4	3.2	71.1	11.6
						95.7	11.0
C. J.	59	Common duct stone	2	4	7.8	59.2	40.0
						102.0	41.7
M. A. C.	41	Common duct stone	4	5	7.4	42.4	9.9
						96.4	12.3
D. F. W.	39	Common duct stone	2	2	5.8	35.7	15.0
						83.3	19.2
P. W.	58	Carcinoma of pancreas	6	3	9.0	28.9	19.6
						96.1	
J. R. B.	53	Carcinoma of pancreas	1.5	6	24.8	83.2	12.5
						100.0	26.6
T. P. H.	66	Carcinoma of pancreas	6	2	5.7	28.0	43.5
						56.7	38.4
M. L. K.	61	Common duct stone	12	5	6.0	70.7	13.1
						100.0	16.7
J. F.	46	Common duct stone	1.5	4	3.2	75.6	6.0
						87.2	1.0
R. M.	75	Carcinoma of pancreas	7	1	0.8	40.5	16.3
						61.1	16.5
M. Y.	34	Biliary fistula		6	7.2	37.5	1.0
						68.9	1.0

* Increase from initial average of 53.4 per cent to 86.2 per cent after treatment; average days of treatment = 3.9; average dose = 6.8 Gm.

In Table II are shown plasma prothrombin concentrations in five patients suffering from massive postoperative hemorrhage. Data from three of these patients are shown graphically in Charts 1, 2 and 3. Patients M. Y., J. R. B. and H. C. K. were given vitamin K-cholic acid mixture immediately and the bleeding ceased with a dramatic rise in plasma prothrombin. Patient T. P. H. developed severe diarrhea when the mixture was given through a

TABLE II

DATA IN CASES OF POSTOPERATIVE BLEEDING*

		Bleeding		
Patient	Operation	Post-operative Day	Plasma Prothrombin Per Cent	Site
T. P. H.	Cholecystostomy	4th	43.7	Urinary and biliary tracts, retroperitoneal tissues
J. R. B.	Cholecystogastrostomy	7th	32.3	Stomach, gallbladder
M. Y.	Repair of common duct	6th	37.5	Wound, gastro-intestinal tract
M. L. K.	Exploratory celiotomy. Biopsy of liver	8th	38.6	Wound, uterus
H. C. K.	Choledochostomy	16th	38.9	Wound, gastro-intestinal tract

* M. L. K. and M. Y. had no vitamin K after operation; J. R. B. and H. C. K. had refused further administration of vitamin K; T. P. H. had developed severe diarrhea; M. Y. had had transfusion of 3,000 cc. of blood during previous 48 hours.

jejunostomy, and the bleeding was uncontrolled. The prothrombin level remained low until the patient succumbed to anuria and liver failure. Patient M. L. K. received no vitamin K-cholic acid mixture after operation owing to the onset of uremic stupor and vomiting. Cirrhosis of the liver, ascites, and

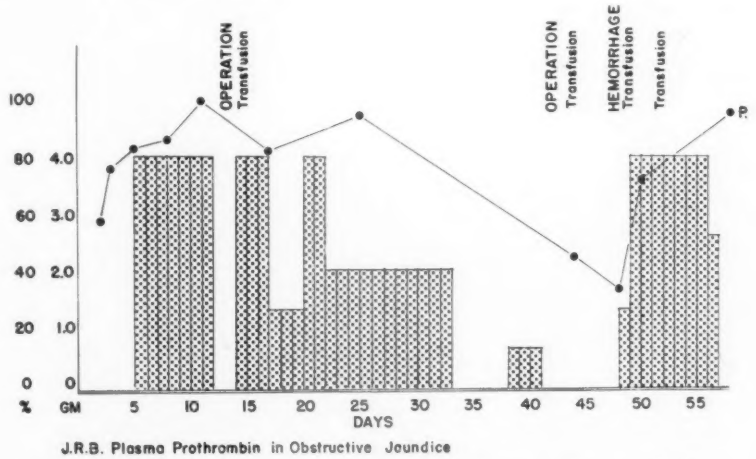

CHART 1.—Patient J. R. B.: Showing plasma prothrombin in relation to varying vitamin K-cholic acid intake and operation. Refusal of patient to take mixture after second operation, leading to fall in prothrombin and massive hemorrhage. First operation was cholecystostomy; the second cholecystogastrostomy; P represents the plasma prothrombin in per cent of normal; the dosage of vitamin K-cholic acid mixture, in grams, is shown in the checkered columns.

anuria made the outlook seem hopeless, and jejunostomy for feeding vitamin K was not performed.

Discussion.—The frequency with which plasma prothrombin is reduced in obstructive jaundice is striking. During the course of this study only one case has been seen in which obstruction to bile flow for over a week

has not been associated with plasma prothrombin levels of less than 84 per cent. In this case the patient's appetite had remained remarkably good and the biliary obstruction was incomplete. In the preoperative group the response

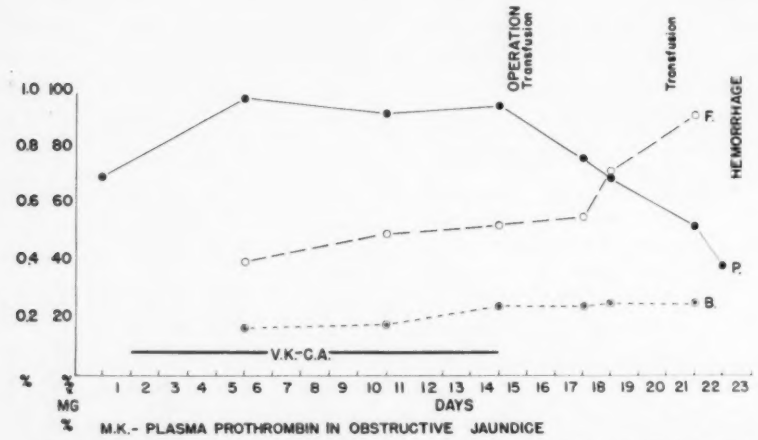

CHART 2.—Patient M. L. K.: Showing plasma prothrombin and fibrinogen in relation to operation and vitamin K-cholic acid intake. Preoperative response to the medication is well shown, with progressive postoperative fall in prothrombin, leading to gross hemorrhage, no vitamin K being taken after operation. The failure of blood transfusion to prevent hemorrhage is obvious. P represents the plasma prothrombin in per cent of normal; F represents the plasma fibrinogen percentage; B represents the plasma bilirubin in milligrams per cent.

to vitamin K-cholic acid has been invariable. It seems to be true, however, that the more severe the liver damage the less marked is the prothrombin recovery. This can be illustrated by data in Table I. Patient T. P. H.

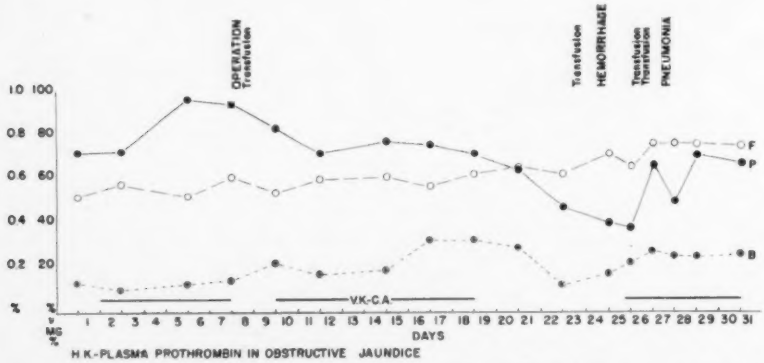

CHART 3.—Patient H. C. K.: Showing the effect of operation, vitamin K-cholic acid mixture and pneumonia on the plasma prothrombin and the fibrinogen. Preoperative response of prothrombin well shown. Note the effect of withdrawal of vitamin K-cholic acid in the presence of persistent jaundice, resulting in massive hemorrhage, with recovery on resumption of vitamin K mixture. Ineffectiveness of transfusion brought out. P represents the plasma prothrombin in per cent of normal; F represents the plasma fibrinogen percentage; B represents the plasma bilirubin in milligrams per cent.

entered the hospital in a moribund state with carcinoma of the pancreas, complete biliary obstruction, liver failure, oliguria, ascites and peripheral edema. The prothrombin response to vitamin K-cholic acid therapy in two days of treatment was only moderate.

Little if any correlation is discernible between the degree of depression of plasma prothrombin and the plasma bilirubin level. This is not surprising since the excretory function of the liver is only one of the factors concerned in the maintenance of plasma prothrombin. Also, even when bilirubin is being excreted, bile deficient in cholic acid and hence less effective in promoting absorption of vitamin K may be formed by the damaged liver.

A drop of 20 to 40 per cent in plasma prothrombin concentration immediately after operation is to be expected, dependent perhaps on such factors as blood loss and dilution of plasma, clotting, and depression of liver function by anoxemia and anesthesia. The fall is transitory, however, if vitamin K-cholic acid feeding is resumed at once. These points are illustrated in Chart 4.

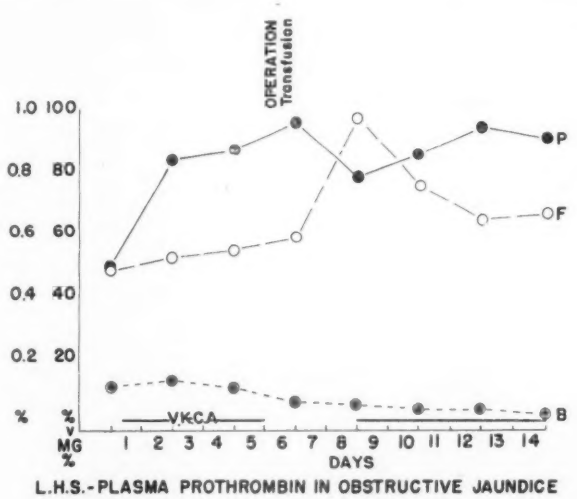

CHART 4.—Patient L. H. S.: Showing the plasma prothrombin in relation to the intake of vitamin K-cholic acid mixture and operation. Postoperative drop with prompt recovery on taking mixture is shown. P represents the plasma prothrombin in per cent of normal; F represents the plasma fibrinogen percentage; B represents the plasma bilirubin in milligrams per cent.

It is apparent that the plasma prothrombin level is quickly responsive to change in metabolic conditions, suggesting the absence of prothrombin reserves in these patients. A safe preoperative plasma prothrombin level, preferably above 75 per cent, is highly desirable. Since the prothrombin level may change quickly, the need for frequent determinations in the early postoperative course, as pointed out by Snell, Butt and Osterberg,[15] is obvious.

In considering the five cases of postoperative hemorrhage, several points stand out. Two patients, J. R. B. and H. C. K., created an interesting experiment by refusing to take the vitamin K-cholic acid capsules after operation on grounds that they caused epigastric distress. In both cases, as shown in Charts 1 and 3, a steady drop in plasma prothrombin with subsequent massive hemorrhage resulted. Thereafter, the patients cooperated in taking the mixture and rapid restoration of plasma prothrombin and cessation of bleeding followed. The biliary obstruction in patient H. C. K. continued

only partially relieved after operation in consequence of cholangeitis, and bleeding set in as late as the sixteenth postoperative day (Chart 3). Undoubtedly the vitamin K, taken for eight days after operation, postponed the bleeding, for, as a rule, bleeding from prothrombin-lack occurs within the first week after operation.

A question of considerable interest, which deserves study, is the influence of infection on plasma prothrombin. There is some evidence that the liver may react sensitively to extrahepatic inflammation, for example, the rise in plasma fibrinogen occurring in the course of abscess formation and in pneumonia. In this connection the data shown in Chart 4 are pertinent. After the plasma prothrombin began to respond to vitamin K-cholic acid therapy following hemorrhage, a bilateral severe pneumonia suddenly set in. The plasma prothrombin level fell, whereas the plasma fibrinogen rose. In Charts 2, 3 and 4 also the lack of relationship between changes in plasma fibrinogen and prothrombin is brought out.

Blood transfusion appears to be a rather inefficient method of combating the bleeding tendency due to hypoprothrombinemia, as the effect on the recipient's plasma prothrombin is slight and transitory. A measurable increase of only 6 per cent occurred in one adult patient whose plasma prothrombin level was determined before and after transfusion of 600 cc. of blood. Blood transfusion is needed to replace lost blood, but vitamin K-cholic acid therapy is indicated in order to prevent further bleeding.

Conclusions

(1) In obstructive jaundice and biliary fistula the plasma prothrombin level may be low.

(2) Following operation upon such patients, further reduction in the plasma prothrombin may occur.

(3) Dangerous bleeding may take place with plasma prothrombin concentration of less than 50 per cent normal.

(4) No correlation can be made out between plasma fibrinogen and prothrombin concentrations.

(5) Administration of a mixture of vitamin K and bile salts, through a jejunostomy if necessary, leads to a restoration of plasma prothrombin and control of the bleeding tendency.

(6) Plasma prothrombin level depends on the functional capacity of the liver as well as absorption of vitamin K from the intestine.

The author wishes to express his gratitude to Dr. H. P. Smith for his courteous help in the details of the prothrombin determination.

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ACUTE HEMATOGENOUS OSTEOMYELITIS OF THE LONG BONES*

A CLINICAL REVIEW OF 160 CASES

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IN SELECTING a topic for the Annual Oration, it seemed fitting to choose one dealing with a condition which is not only frequently encountered by both surgeon and internist and about which there exists a considerable difference of opinion as to the choice of treatment, but also one in which, regardless of the method of therapy employed, the mortality is still far greater than it should be; namely, acute hematogenous osteomyelitis.

This mortality is all the more lamentable because in few other major surgical conditions should a diagnosis be made more readily, since in the vast majority of cases the patient seeks medical relief within a short time of the onset of the disease, hence, failure to obtain a satisfactory result can seldom be attributed to procrastination on the part of the patient—this facor only too often being exhibited rather by the physician who first sees the case.

Aside from the question of mortality, when one considers the degree of morbidity which so frequently accompanies this condition, whether it be deformity of the involved limb or limbs, ankylosis of joints, or persistence of infection as exemplified by long delayed and residual sequestration, chronic pyogenic infection, *etc.*, one can readily appreciate the importance of the early institution of that method of treatment by which these sequelae may best be avoided.

That a wide difference of opinion exists as to the most satisfactory method of handling acute hematogenous osteomyelitis, is shown by the voluminous literature which has appeared on the subject, especially in recent years, after even a cursory review of which one is left in rather considerable doubt as to just what is the best method of handling this condition.

In the hope that it might be possible to help, in even a very minor degree, in the solution of the clinical aspect of this problem, we have examined the records of 160 cases of acute osteomyelitis compiled from the records of the Pennsylvania, Graduate, Childrens, Presbyterian and Germantown Hospitals in Philadelphia, and the Bryn Mawr and Burlington County Hospitals.†

It is not within the scope of this paper to review in detail the etiology, pathology and symptoms of acute osteomyelitis, as this information is readily

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available in any of the numerous publications on the subject, but rather in this respect, merely to briefly mention a few of the more salient factors which should be borne in mind when called upon to treat this condition.

This communication is limited to a discussion of that form of acute osteomyelitis of the long bones which occurs chiefly in children and young adults, is blood borne in distribution, and is caused most frequently by some form of Staphylococcus or Streptococcus or both, and occasionally by the pneumococcus or *Bacillus typhosus.* It does not include those cases associated with compound fracture nor the more indolent types of infection, such as tuberculosis and syphilis, and that encountered in Brodie's abscess nor the sclerosing osteomyelitis of Garre.

Acute hematogenous osteomyelitis may be regarded as a more or less rapidly developing osseous inflammation resulting from a blood borne infection, in which the bacteria usually lodge in that portion of the cancellous part of the metaphysis abutting upon the epiphysis. This region of bone, being richly supplied by terminal capillary loops and the blood current being slowed in this capillary bed, readily affords the organisms an opportunity to settle in this locality.

In this connection, Fraser advances the theory that localization of an abscess in the bone marrow, although creating a difficult and regrettable situation as far as the local infection and suppuration are concerned, may have a salutary effect, as it may be the body's method of producing a defensive area from which the factors of immunity may be developed. He argues that a general blood borne infection may have less serious consequences if the infection becomes localized in a bone abscess.

The experimental work of Lexer, to which reference is made by many writers, is also of interest in this respect, as he showed that the introduction of large numbers of bacteria into the blood stream of experimental animals produces death within 24 hours, without abscess formation. When suspensions of less virulence and weaker concentration were introduced in the same manner, the tendency was to produce abscesses in the various tissues, and the bone was most apt to be involved as the concentration and virulence of the organisms were decreased.

In the human being, invasion is characterized by a tendency to rapid spread, the infection soon appearing and extending beneath the periosteum which becomes elevated from the shaft of the bone. By involving the haversian system and occluding its vessels, the infection causes an extending necrosis of the bone, and reaches the medullary cavity either by way of the haversian system, extension backward from the original focus through the cancellous part of the metaphysis, or both. Perforation of the periosteum results in soft tissue abscess with its resultant signs and symptoms.

Due to the dense attachment of the periosteum to the tough epiphyseal plate, when the infection reaches the periosteum it is directed away from the epiphysis and it is usually only in the late stages of the disease that the latter, and subsequently the joint, become involved. The fact that the epiphysis re-

ceives its blood supply from a source independent of that of the shaft of the bone—branches of the articular vessels entering its surface—further tends to exclude it from involvement by an infection borne by the nutrient artery of the shaft. Concurrently with the bone invasion, there is usually a more or less profound systemic toxemia which may either rapidly prove fatal or, should it become chronic, may exhaust the patient with its complications and sequelae.

Most of the reported series of cases show a higher incidence of the disease in males—possibly due to their being more subject to local trauma and infection, such as cuts, bruises, abrasions, *etc.*, nor, in this respect, should one fail to make due allowance for exposure to cold and wet. While the condition may occur at any time from birth up to the age of fusion of the epiphysis or later, its most frequent occurrence is noted between the ages of 3 and 18.

A fact not generally appreciated and well stressed by Green, is that osteomyelitis in infants under two years of age presents quite a different picture from that seen in older children, in that in the former, the infecting organism is more apt to be the Streptococcus rather than the Staphylococcus; the course being of brief rather than of long duration; the wound tends to heal rapidly rather than slowly; sequestration is infrequent rather than usual; recurrences are rare in contrast to being frequent in the older children, and the lesions usually heal completely instead of leaving a residual sclerosis of bone. The cases reported by Green and others show that the younger the infant the higher is the mortality. In the present series the age incidence was from six weeks to 50 years.

While it is true that any pus producing organism may cause osteomyelitis, yet in the vast majority of cases some form of the Staphylococcus, being the most frequently encountered pus producing skin organism, is most often the offending agent. In the present series, when the Streptococcus was encountered, it was usually associated with a focus in the pharynx, middle ear or sinuses, and a mixed infection was by no means an infrequent occurrence.

There is considerable difference of opinion as to the part that trauma exerts in localizing the lesion. The conclusion drawn by Farr would tend to belittle this as a causative factor, as he states that there is a history of injury in only about one-third of the cases, and it is often of such a trivial nature that there is no evidence of its presence at the time the patient comes under observation. He also draws attention to the fact that the part of the bone in which the infection starts is usually well protected. This latter statement, however, would not necessarily be the case in involvement of the tibia, which, in the series we are reporting, was the bone most frequently involved. Farr believes it quite likely that trauma merely focuses attention to the part involved, as is noted in other conditions—for example, cancer of the breast.

In this connection, the work of Baudet and Cahuzac is of interest. Experimenting upon rabbits, into which Staphylococci were injected intravenously, subperiosteally and into the metaphysis, they were unable to produce bone infection by the intravenous route even after the bone (tibia) had been traum-

atized, but infection was produced by the subperiosteal and intrametaphyseal injection, the resulting osteomyelitis, however, in no way resembling that seen in either children or adults. They further observed that when reparation of the lesion began, the blood calcium immediately decreased, as if all the resources of calcium in the body were being mobilized at the point where they were needed for the healing process. They found that the blood calcium rose gradually as the healing process progressed, and when healing was complete, it had attained normal levels. They believe that this suggests that when the blood calcium was no longer required for reparative processes in the bone it was released into the general circulation. They suggest that these findings would indicate that in osteomyelitis, estimation of the blood calcium might be of aid in determining the most opportune time for resection, which would be when the blood calcium reached its lowest level, indicating that the regenerative processes in the bone at this time are at maximum.

Earlier in this presentation, the statement was made that the diagnosis of acute osteomyelitis should not present any particular difficulty, providing the possibility of its occurrence be constantly kept in mind. While this statement holds true in the vast majority of cases, an exception may be noted in the case of infants when, as cited by Farr, the patient cannot be of much assistance in aiding the examiner to localize the site of the lesion—for example, those instances in which the onset of local edema is rapid, and the limb, when first seen, presents a swelling of the entire extremity, originating from a single focus in the bone, this occurring even in spite of the periosteum not being perforated. Under such circumstances, it is not unusual to find the swelling and tenderness, although maximal at the suspected site of the lesion, yet not sufficiently circumscribed to accurately define the area involved.

While it is also true that in most instances the signs and symptoms of acute hematogenous osteomyelitis are rather typical, yet it is in those cases presenting atypical features that one is apt to make a diagnostic error unless the condition is suspected and sought for. Among the more frequently encountered diagnostic pitfalls, perhaps acute rheumatic fever and local cellulitis head the list, and in infants one should not fail to consider joint sepsis, scurvy and occasionally hemarthrosis.

As an aid in the differential diagnosis between local cellulitis and acute osteomyelitis, we have found that the old observation of the response to continuous digital pressure over the suspected area has frequently been of considerable assistance. Should the condition be a simple cellulitis without bony involvement, the maximum discomfort of the patient is experienced when the digital pressure is first applied, and while further deep pressure causes some discomfort, it is not marked. Should the condition be osteomyelitis, the reverse is true; namely, while the initial pressure may be somewhat painful, its continuation causes an increase of pain out of proportion to the force applied. This simple expedient has been of value in cases in which, for instance, the patient has an infected lesion of the foot and one wishes to determine whether

the inflammatory reaction over the tibial area draining this region is a simple cellulitis or an acute osteomyelitis.

It is well to bear in mind the fact, as stated by Homans and others, that the site in which symptoms first appear is not necessarily that in which the disease will develop. Thus, the child may have complained of pain in the region of one or more joints before developing the acute localizing lesion, these preliminary manifestations tending to confuse the picture with that of acute rheumatic fever. While it is true that acute osteomyelitis occurs most frequently in the long bones, one should bear in mind the possibility of its developing in the flat ones as well, notably the scapula and pelvis where, in the latter, it may simulate hip disease. When the condition appears in the skull it is most apt to follow an infected injury and may involve either the outer, or both tables of bone.

One may briefly summarize the question of diagnosis by stating that failure in this respect may most frequently be attributed to the fact that the condition is unsuspected.

The author is not in accord with the statement by Cutting, that "if the diagnosis is made sufficiently early and the proper treatment is then instituted, the mortality in osteomyelitis should be nil." Cutting's conclusion may be true in those instances in which a single localized focus is the only lesion, but we do not believe it can be maintained where this focus is an incidental local manifestation of an overwhelming blood stream infection. In this respect, our experience has been more in accord with that of Wilensky, who states that "every case of osteomyelitis is basically composed of two components—a general bacterial infection, be it sepsis, septicemia or bacteremia, and a local lesion in the bone tissue."

We also concur with the latter's opinion that, in the treatment of the condition in the early stages, the most important item is the general infection, and that "the ultimate outcome—death or recovery—is dependent on this above mentioned factor, and the mortality statistics of acute hematogenous osteomyelitis in its early stages reflects accurately the mortality of a general bacterial infection. When divorced from the general bacterial infection, and in the absence of any fatal complications or associated lesions, the mortality of the osseous lesion is nil." In conjunction with the above statement, one should bear in mind the possibility of converting a local lesion into an infection of the blood stream by inopportune or misdirected operative efforts.

In discussing treatment, about the only, even partial, accord one can find among various authors is as regards prophylaxis in the elimination of foci of infection throughout the body, and the avoidance of those factors such as trauma, strain, chilling, *etc.*, which may be classed as physiologic attributes. The widest diversity of opinion exists as to the time and character of treatment of the local lesion, ranging from what might be classed as ultra-conservatism—purely supportive treatment with the exclusion of surgical procedures—to radical drainage, as exemplified by extensive guttering of

the involved area, or even resection of the shaft from one epiphysis to the other.

Thus, to cite but a few of the many diversified opinions in this respect, Kulowski advocates operating just as soon as the diagnosis is made, regardless of whether the condition is acute, chronic, or presents any other unusual phases of the disease. His main argument centers on the fact that pyogenic osteomyelitis is essentially a most devastating disease, which must be combated by bold, aggressive, radical operative measures. He believes that there is no proof that direct drainage of the bone in the acute stage increases the death rate, and is convinced that the vast majority of cases are undertreated. As one becomes more and more familiar with the disease, in his opinion, one is the more ready to adopt the most radical measures to attain a cure. In 92 cases of osteomyelitis of the femur, he reports a mortality of 3 per cent, and there was no mortality among 80 cases of involvement of the tibia—truly a remarkable record, which was unsurpassed by any other statistics we could find.

In a collected review of the subject, Cutting states that the operative treatment of the condition must always be considered an emergency procedure in which minutes count, and a delay of hours may mean the difference between life and death. He further is of the opinion that an operation performed at the earliest possible moment in these cases, even if performed by unskilled hands, is undoubtedly to be preferred to any considerable delay, provided the operative procedure is rational. Other things being equal, one who undertakes the treatment of a case of acute osteomyelitis may be forgiven if his treatment is a little too radical, but may not be forgiven if his treatment is insufficient. Among his conclusions, Cutting states: "If, in a given case, there is doubt as to whether operation should be performed or not, a safe rule to follow is to paraphrase an aphorism coined with respect to drainage in abdominal surgery—when in doubt, operate."

Pyrah and Pain also advocate early radical surgery, reporting a 29 per cent mortality in 176 cases, and a 27 per cent mortality in 262 cases.

Buzellow, in 1928, advocated chiseling open the marrow cavity as soon as possible, and believes that blood stream infection or general sepsis can be avoided only by the early evacuation of pus. He states that the results in his clinic compare favorably with those in which the marrow cavity was not opened. Other authors, advocating early drainage of the bone, regardless of the patient's condition, express essentially the same views as those quoted.

Among those favoring conservative measures may be mentioned Philipowicz, who believes that the treatment depends upon whether the course of the disease from the beginning has the distinct character of an acute, severe infectious disease, or is that of a localized and more or less circumscribed bone disease; and that treatment should be basically conservative without opening the bone; abscesses to be merely incised. He is of the opinion that

the problem in the acute stage cannot be solved by operation alone, and advocates the use of serum and vaccine from the onset.

Miller and Smith-Petersen, reporting a series of 90 cases, state that they are becoming more conservative in their treatment of the acute cases, and attack the local lesion only after the patient's condition has been rendered as favorable as possible. Should an abscess be present, it is merely incised, and where pus in the bone is suspected, they only drill a few holes.

Wilson and McKeever, reporting 90 cases, with 12.2 per cent mortality, are of the opinion that operation may be performed too early rather than too late. Of 24 patients having early adequate drainage within seven days of the onset of the illness, 25 per cent died. These showed no microscopic evidence of osteomyelitis. When operation was delayed until between the seventh and twenty-eighth day, the mortality was 9.7 per cent. In 23 cases of spontaneous drainage, there was only one death. Of the 24 cases operated upon in the early stages of the disease, 37.5 per cent developed metastatic lesions. In their summary, they state that operation should be delayed until the child is in the best condition (one, two or three days), and that, in a blood borne infection, the lesion should be allowed to localize. If operated upon too early, a fatality may result, as in incision in cases with brawny cellulitis.

Leveuf states that, in his experience, late intervention as a rule gave better results than early operation, and believes that the criterion of progress is the temperature and blood culture. He found that a septicemic state was of no grave prognostic significance, for in all of his cases in which operation was not performed, early spontaneous recovery ensued and no foci developed. He found that a subperiosteal abscess usually forms as the temperature falls and is related to a central focus in the diaphysis and that early surgery establishes a communication between the focus in the bone containing virulent organisms and toxins, and parts of the body in which the defense mechanism is not yet established. He found that late intervention does not aggravate the osseous lesions or process of sequestration. He further states that the advantage of conservative treatment cannot be over emphasized, and that vaccine therapy should be administered.

Crossan presented the results of early and late intervention in a series of cases, in which the lower mortality was decidedly in favor of conservative treatment.

As a working method in deciding upon the form of treatment indicated in specific cases, the classification of Wilensky forms a satisfactory guide: Group I. Cases in which operation of any kind can be avoided. These, with their subgroups, consist essentially of the milder forms of the disease. Group II. Includes those cases in which the general infection is the paramount factor and determines the fatal end-result. This is the most virulent group, and operation can be of little avail. Group III. Those cases in which the general infection becomes controlled and the end-result depends entirely on the local lesion or any intercurrent complication or associated lesion. Group

IV. That in which the general infection becomes controlled and the end-result depends entirely on the local lesion in the bone.

Unfortunately, the data as presented in the histories of the present series are not sufficient to enable us to classify our cases in accord with the above suggestion, and in a series such as this, collected from various hospitals, it has been necessary to arbitrarily establish certain criteria, especially as this communication deals chiefly with the clinical aspects of the condition.

With this in mind, and appreciating its limitations, we wish to present the results of our studies from the following aspects:

I. The outcome (survived or died) in relation to: (1) The age of the patient; (2) the degree of toxicity of the patient at the time of operation, described as very toxic, or slightly so; (3) the operative procedure employed, whether (a) mere incision or aspiration, (b) drill, or (c) gouge or guttering of bone, and (d) time of operation. A patient was arbitrarily regarded as being toxic when the temperature was over 102° F., with corresponding increase of pulse rate and leukocytosis, and presented the general appearance of toxemia. Operation was classed as immediate, when performed within 48 hours of making the diagnosis, and delayed, when performed at any time after the second day.

II. The results in relation to: (1) Type of organism; (2) with reference to the time of operation, (a) early, (b) delayed; (3) the operative procedure, whether the bone was opened by drill or gouge, or merely aspiration, incision, or no surgical procedure; (4) the site of the infection, whether (a) only in the original site, (b) in the blood stream alone, (c) primarily in the original site and blood stream, or (d) primarily in the wound and secondarily in the blood stream after operation.

III. The formation of secondary foci and the outcome in reference to: (1) The type of organism; (2) the time of operation.

IV. The outcome in reference to: (1) The age of the patient; (2) the bone involved; and (3) the time of operation.

V. The formation of sequestra as related to: (1) The time of operation; and (2) the type of infecting organism.

Table I shows, that of 17 cases under three years of age, six were very toxic when operated upon. Of these, immediate drilling was performed in one case, with recovery; the bone was opened twice with a gouge, with recovery; delayed drilling was performed in three instances, with recovery, and one child who died was so ill that no operative procedure was attempted. Of the children under the age of three, who were only slightly toxic when seen, drilling was performed immediately in one and gouging in two, all of whom lived. In the delayed group, drilling was performed in two, and the gouge used in five, all of whom survived.

Between the ages of three and nine, the statistics for the very toxic group, with immediate operation, were 11 drilled and 14 gouged, of whom one drilled and six gouged died. Four, who were not operated upon or incised, lived and two died. In this age group (three to nine), when the patient was only slightly

TABLE I

RESULTS OF IMMEDIATE AND DELAYED OPERATIONS IN REFERENCE TO AGE, DEGREE OF TOXICITY, AND OPERATIVE PROCEDURE

Age	Toxicity	Operative Procedure	Immediate Operation		Delayed Operation		Not Operated, Incised, *etc.*	
			Lived	Died	Lived	Died	Lived	Died
Under 3 yrs.	Very	Drill	1		3			1
		Gouge	2					
	Slight	Drill	1		2			
		Gouge	2		5			
3–9	Very	Drill	10	1	2		4	2
		Gouge	8	6	3	1		
	Slight	Drill	5		2		6	
		Gouge	6	1	10			
10–14	Very	Drill	2	10	2		1	
		Gouge	13	2	1	2		
	Slight	Drill	3		1		4	
		Gouge	4		7			
15–19	Very	Drill			1			
		Gouge	1	3	1			
	Slight	Drill			1			
		Gouge	2		6			
Over 20	Very	Drill				2		
		Gouge						
	Slight	Drill						
		Gouge	1		5	1		
	Totals		61	23	52	6	15	3

	Number of Cases	Deaths	Percentage Mortality
Very toxic, immediate operation—drill	24	11	45.8
Very toxic, immediate operation—gouge	35	11	31.4
Slightly toxic, immediate operation—drill	9	0	0
Slightly toxic, immediate operation—gouge	16	1	6.2
Very toxic, delayed operation—drill	10	2	20.2
Very toxic, delayed operation—gouge	8	3	37.5
Slightly toxic, delayed operation—drill	6	0	0
Slightly toxic, delayed operation—gouge	34	1	2.9
No operation, toxic	18	3	16.6
Totals	160	32	

toxic, and was immediately operated upon, of those who survived, five were drilled, with no mortality, and of the seven in whom the gouge was employed, one died. When operation was delayed in the slightly toxic, of those who

lived, six were aspirated or incised, two drilled and ten gouged, with no mortality.

Between ages 10 and 14: Very toxic, immediate operation—two drilled and 13 gouged, survived; while 10 drilled and two gouged, succumbed. Very toxic, delayed operation—two drilled and one gouged, survived; while two gouged, died. Slightly toxic, immediate operation—the three drilled and four gouged, all survived. Slightly toxic, delayed operation—one drilled, seven gouged and four incised or aspirated, all survived.

Between ages 15 and 19: Very toxic, immediate operation—of the four upon whom the gouge was used, one lived and three died. Delayed operation in this group showed one gouged and one drilled, with no mortality. Slightly toxic, immediate operation—two gouged, lived, no mortality. Delayed operation—one drilled and six gouged, lived, no mortality.

Over 20 years of age. The only two very toxic cases, who were drilled late, died, and of those only slightly toxic, one immediate operation, gouge, lived, and of the delayed operations, gouge, five lived and one died.

TABLE II

MORTALITY PERCENTAGE OF ENTIRE GROUP IN REFERENCE TO CONDITION OF PATIENT, AND TIME OF OPERATION

		Deaths*	Lived	Percentage Mortality
Toxic	Immediate operation	22	37	37.3
	Delayed operation	5	13	27.7
Nontoxic	Immediate operation	1	24	4.0
	Delayed operation	1	39	2.5

* Not included in above summary:
Two moribund on admission—not operated upon.
One death from hemorrhage upon removal of sequestrum, 3 yrs. later.
One death from hemorrhage upon removal of sequestrum, 3½ mos. later.
Deaths from hemorrhage (several) on thirty-ninth day.

Table II gives the summary of the fatalities in this series, and contracts immediate versus delayed operation (disregarding the operative procedure), in the toxic and nontoxic patient, regardless of age, type of organism or operative proceeding and shows that in 59 toxic patients, upon whom immediate operation was performed, 37 lived and 22 died, a mortality of 37.3 per cent; while of the 18 toxic cases, in whom operation was delayed, 13 lived and 5 died, a mortality of 27.7 per cent. In the nontoxic patients, of the 25, upon whom immediate operation was performed, 24 lived and one died, the figures for the delayed, nontoxic, total 40, of whom 39 lived and one died, a mortality of 2.5 per cent. Not included in the above figures are two patients who were moribund on admission and upon whom no operative procedure was performed; two who died from hemorrhage upon removal of a sequestrum, one, three years, and one, three and one-half months after the original operation, and one patient, who died on the thirty-ninth postoperative day as a result of uncontrolled hemorrhage. A consideration of the above statistics

does not leave much room for doubt that, at least in this series, immediate operation in the very toxic patient showed a higher mortality, in contrast to those instances in which operation was delayed.

In only two instances did the records show that upon admission the patients were moribund and any operative procedure considered inadvisable, while upon several occasions the notes stated "patient moribund—operation—death within a few hours."

TABLE III

OUTCOME IN REFERENCE TO DEVELOPMENT OF SECONDARY FOCI, THE TYPE OF ORGANISM, AND TIME OF OPERATION

	Developed Foci						Did Not Develop Foci					
	Early Operation		Delayed Operation		Not Operated Upon, Aspirated or Incised		Early Operation		Delayed Operation		Not Operated Upon, Aspirated or Incised	
	Lived	Died	Lived	Died	Lived	Died	Lived	Died	Lived	Died	Lived	Died
Staphylococcus	19	7	7	1		1	42	11	13	3		3
Streptococcus	5	1					5		2			
Others or mixed							2					
Not recorded or no growths	2	2	1				9	1	13	1		1
Totals	26	10	8	1		1	58	12	28	4		4
Totals	36		9		1		70		32		4	
Died	10		1		1		12		4		4	
Mortality percentage	27.7		11.1		100		17.1		12.5		100	

SECONDARY FOCI

Developed	Early Operation	Delayed Operation
Yes	36 (33.9%)	9 (21.9%)
No	70 (66.1%)	32 (78.1%)

Among the reasons advanced for the early surgical interference is that by so doing, there is a decrease in the number of secondary foci which may develop. Table III shows that of the cases in which, regardless of the degree of toxicity, it could be ascertained from the notes as to whether or not such foci developed, these occurred in 33.9 per cent of the cases in which operation was performed early, and in 21.9 per cent of the cases in which it was delayed. Of the 36 cases developing secondary foci, who were operated upon early, 10 died, a mortality of 27.7 per cent, while of the nine who were operated upon later, only one died, a mortality of 11.1 per cent. Of the 70 cases who were operated upon early, and who did not develop secondary foci, 12 died, a mortality of 17.1 per cent; and of the 32 who did not develop secondary foci and were operated upon later, four died, a mortality of 12.5 per cent. From the above it will be seen that early operation does not tend to prevent the development of secondary foci, and when such foci appear, the mortality is 27.7 per cent in contrast to 11.1 per cent when such foci appear following the delayed operation. When there were no secondary foci, the

TABLE IV

MORTALITY IN REFERENCE TO PRIMARY BONE INVOLVEMENT, AGE OF PATIENT, AND TIME OF OPERATION

AGE	HUMERUS						RADIUS OR ULNA						FEMUR						TIBIA						FIBULA					
	Early Op.		Del. Op.		Not Op., Asp., or Inc.		Early Op.		Del. Op.		Not Op., Asp., or Inc.		Early Op.		Del. Op.		Not Op., Asp., or Inc.		Early Op.		Del. Op.		Not Op., Asp., or Inc.		Early Op.		Del. Op.		Not Op., Asp., or Inc.	
	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D
Under 3 yrs.	1		2				1						1		5				1		2		1		1					
3–9	2				2	1	3		1				11	2	6	1	2	1	14	6	7		2		4		3	1		
10–14	1	1							1				5	3	6	1	2		15	7	3		1		3		1			
15–19		1	1										1	2	4				1		3						2			
Over 20			2	1									1		1	3					3									
Totals	4	2	5	1	2	1	4	0	2	0	0	0	19	7	22	5	4	1	31	13	18	0	3	1	8	0	6	1	0	0
Totals			15						6						58						66						15			
Died			4						0						13						14						1			
Mortality percentage			26.6						0						22						21						6.6			

FEMUR—Early operation, 26 total, 7 deaths, 26.9% mortality
Delayed operation, 27 total, 5 deaths, 18.5% mortality
Aspirated or incised, 5 total, 1 death, 20 % mortality

TIBIA —Early operation, 44 total, 13 deaths, 29.3% mortality
Delayed operation, 18 total, 0 deaths, 0 mortality
Aspirated or incised, 4 total, 1 death, 25 % mortality

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mortality of early interference was 17.1 per cent in contrast to 12.5 per cent when delayed.

Table IV shows the age of the patient, the primary bone involved, the time of operation, and the end-result. It will be seen that the femur and tibia were the bones most frequently involved, and in the 26 instances in which early operation was performed upon the femur, there were seven deaths, a mortality of 26.9 per cent, while of the 27 delayed instances, there were five deaths, 18.5 per cent mortality. The statistics for the tibia are even more striking, for in the 44 cases with early operation there were 13 deaths, a mortality of 29.3 per cent, while in 18 in which operation was delayed, there were no deaths.

TABLE V

FORMATION OF SEQUESTRA IN REFERENCE TO TYPE OF ORGANISMS AND TIME OF OPERATION

Time of Operation	Organism	Sequestra Removed: Yes	Sequestra Removed: No	Percentage Developing Sequestra
Early	Staphylococcus	17	53	24.2
	Streptococcus		5	0
	No growth or not stated	3	8	27.2
	Other or mixed		3	0
Delayed	Staphylococcus	16	30	34.7
	Streptococcus		4	0
	No growth or not stated	1	8	11.1
	Other or mixed		1	0
No operation, aspirated or incised	Staphylococcus	1	5	16.6
	Streptococcus		1	0
	No growth or not stated		4	0
	Other or mixed			

SEQUESTRA

Operation	Developed: Yes	Developed: No
Early	20 22.4%	69 77.5%
Later	17 28.3%	43 71.5%
Not operated upon	1 9.1%	10 90.9%

The statistics were studied with regard to the formation of sequestra, in conjunction with the time of operation and the invading organism, and Table V shows that the time of operation had but little effect on the formation of sequestra—22.4 per cent in the early cases and 28.3 per cent in the late. As was to be expected, the Staphylococcus was the most frequently encountered organism. The outcome was studied from the viewpoint of the operative procedure; whether the bone was opened by drill or gouge, as related to the time of operation and the condition of the patient. Table VI

TABLE VI

	Number of Cases	Deaths	Percentage Mortality
Very toxic, immediate operation—drill	24	11	45.8
Very toxic, immediate operation—gouge	35	11	31.4
Slightly toxic, immediate operation—drill	9	0	0
Slightly toxic, immediate operation—gouge	16	1	6.2
Very toxic, delayed operation—drill	10	2	20.0
Very toxic, delayed operation—gouge	8	3	37.5
Slightly toxic, delayed operation—drill	6	0	0
Slightly toxic, delayed operation—gouge	34	1	2.9
No operation	18	3	16.6
Totals	160	32	

shows that in the very toxic, a higher mortality accompanied immediate drilling of the bone, 45.8 per cent, than when the gouge was used, 31.4 per cent, the difference probably being due to the more toxic state of the patient when the drill was employed. When the operation was delayed in the very toxic, the mortality percentages were reversed, the drill being 20 per cent and the gouge 37.5 per cent. When the patient was only slightly toxic, immediate drilling was resorted to nine times, without a fatality, and the gouge employed 16 times with one fatality, 6.2 per cent, while when the patient was only slightly toxic and operation delayed, in six instances the bone was drilled without fatality, and opened by gouge 34 times with one fatality, 2.9 per cent. When the operative procedure was incision, aspiration or no surgical interference, three of 18 cases died, a mortality of 16.6 per cent. In this latter group are included the two who were moribund when first seen and who died within a few hours of admission to the hospital. From an analysis of the above table, it is again evident that surgical interference in the very toxic patient, whether immediate or delayed, and regardless of the procedure adopted, is accompanied by a much greater mortality than when surgery is postponed until the patient is no longer in a toxic condition—33.6 per cent contrast to 2.2 per cent; it being fully realized, however, that some patients are so overwhelmed by their toxemia that they will succumb in spite of any form of treatment.

Table VII shows the elapsed time, in the fatal cases, between operation and death, in reference to the age of the patient, the degree of toxicity when operated upon and the time of operation. The two cases, which were moribund on admission and which were not operated upon, are not included. It will be seen that the greatest number of fatalities occurred within the first four days, all but one of which were in the toxic group who were immediately operated upon. In the three cases dying from hemorrhage, one month or longer after operation, the condition of the patient and time of operation probably had but little bearing on the outcome, but they are nevertheless included. The conclusion to be drawn from the statistics in this table is that the toxic patient immediately operated upon was not afforded sufficient opportunity to combat the infection. The only two fatalities in the nontoxic, de-

TABLE VII

ELAPSED TIME BETWEEN OPERATION AND DEATH IN REFERENCE TO AGE, CONDITION OF PATIENT, AND TIME OF OPERATION

Age	Condition	Time of Operation	Interval Between Operation and Death									
			Days							2nd Week	3rd Week	Over 3 Weeks
			1	2	3	4	5	6	7			
Under 3 yrs.	Toxic	Immediate	1									
		Delayed										
	Nontoxic	Immediate										
		Delayed										
3–9	Toxic	Immediate		2	2	1					1	2
		Delayed								1		
	Nontoxic	Immediate					1					
		Delayed									1	
10–14	Toxic	Immediate	4		3	1		1		2		1
		Delayed										
	Nontoxic	Immediate										
		Delayed										
15–19	Toxic	Immediate	1	1								
		Delayed										1
	Nontoxic	Immediate										
		Delayed										
Over 20 yrs.	Toxic	Immediate										
		Delayed			1							1
	Nontoxic	Immediate										
		Delayed										1
Totals			6	3	6	2	1	1	0	3	2	6

Two cases moribund on admission—not operated upon—not included.
One died from hemorrhage upon removal of sequestrum, 3 yrs. later.
One died from hemorrhage upon removal of sequestrum, 3 mos. later.
One died from multiple hemorrhages, upon removal of sequestrum, 39 days later.

	Days							Weeks		Over 3 Weeks	
	1	2	3	4	5	6	7	2	3		
Toxic, immediate	6	3	5	2	1	1	0	2	1	3	28 Total
Toxic, delayed	0	0	1	0	0	0	0	1	0	2	
Nontoxic, immediate											2 Total
Nontoxic, delayed									1	1	
	6	3	6	2	1	1	0	3	2	6	
Totals	17				2			11			

layed operation group, occurred as a result of secondary hemorrhage in the third week or later.

An attempt was made to evaluate the hospital morbidity in the series, but in view of the fact that there was no basis of estimating how long the patients should be hospitalized, this attempt was abandoned. The records showed that in many instances a patient was readmitted one or more times for involvement of the original or other sites, but in the series being reported, only the first admission was considered.

TABLE VIII

OUTCOME IN REFERENCE TO LOCATION OF INFECTION, ORGANISM, AND TIME OF OPERATION

Organism	Time of Operation	Wound Only		Blood Only		Both Primary		Primary Wound Secondary Blood	
		Lived	Died	Lived	Died	Lived	Died	Lived	Died
Staphylococcus	Early	34	6			7	6	8	9
	Delayed	39	1			2	4		1
	Not operated upon or incised	5		1			1		
Streptococcus	Early	3						1	
	Delayed	2				1		1	
	Not operated upon or incised							1	
Other or mixed	Early	3							1
	Delayed								
	Not operated upon or incised								
Totals		86	7	1	0	10	11	11	11
No organism, or not recorded	Early	7	1						
	Delayed	8	1						
	Not operated upon or incised	1	1						
Totals		16	3						

Wound only: Incised, 5 cases—all lived
Wound only: Early operation, 46 cases—6 died— 13 % mortality
Wound only: Delayed operation, 42 cases—1 died— 2.3% mortality
Both primary: Early operation, 13 cases—6 died— 46.1% mortality
Both primary: Delayed operation, 7 cases—4 died— 57.1% mortality
Primary Wound—Secondary Blood: Early operation, 19 cases—10 died— 52.6% mortality
Primary Wound—Secondary Blood: Delayed operation, 2 cases—1 died—50 % mortality

Table VIII shows the results in reference to the site of the primary infection, in relation to the type of organism, and to the time of operation. It will be seen that in the majority of cases in which the organism was identified, when the infection was confined to the original focus (93 cases), there were seven deaths, a 7.5 per cent mortality, regardless of the time of operation. In this group of the 46 cases subjected to early operation, six died, a mortality of 13 per cent, while of the 42 with delayed operation, one died, a mortality

of 2.3 per cent. Of the five in this group, in which the operative procedure was limited to incision, there were no deaths. When the infection was primary in both blood stream and bone, of the 13 operated upon early, six died, a mortality of 46.1 per cent; and of the seven who were operated upon later, four died, a mortality of 57.1 per cent. When the infection was primarily in the wound and the blood stream showed involvement after early operation, 10 of the 19 cases operated upon died, a mortality of 52.6 per cent. In the two cases of primary wound and secondary blood stream infection following delayed operation, the mortality was 50 per cent.

The above statistics would tend to show that when the infectious process was confined to the primary site the mortality was considerably less when operation was delayed than when performed early, 2.3 per cent as compared to 13.9 per cent. When the blood stream was involved together with the bone at the time of operation, the mortality was exceptionally high, regardless of the time of operation—46.1 per cent for early and 57.1 per cent for late.

While it is generally agreed that the Orr method of treatment, or some modification of it, affords the best results after the bone has been drained, a careful follow-up record in this respect was not obtained in the present series in a sufficient number of cases to warrant an opinion based on statistics. No attempt was made, therefore, to estimate the morbidity as related to the various methods of treatment adopted, but in our own experience the method advocated by Orr has given greater satisfaction than any other.

In a small proportion of cases, too few to warrant classification, various types of vaccine and bacteriophage were administered, but an estimation of their efficacy would be of doubtful value from the data supplied. Likewise, even though blood transusions, both single and multiple, large and small, were given in many cases, one would not be justified in evaluating their effect in view of the many other factors encountered in each case. As a general impression, not verified by statistical evidence, we feel that repeated, small blood transfusions are well worth while, as if properly given, apparently they can do no harm and might be of considerable assistance in rendering the patient better able to overcome his infection.

In view of the fact that the old saying still holds that experience is a hard task master, and also that we learn most from our mistakes, a very brief comment on some of the fatalities which occurred might be of interest: A female, age 13, treated for rheumatism for five weeks before the osteomyelitis was suspected, died of shock when a sequestrum was removed from her femur, three and one-half months after the original operation. The notes state that her hemoglobin was never above 52 per cent until just after a transfusion which preceded the sequestrectomy, and "at this date it looks as though earlier and frequent transfusions might have saved her."

A boy, age 12, moribund on admission, three days after onset, was immediately operated upon. The notes state: "Operation (drill) very short, only 15 minutes. Death next day." This was obviously a case in which no improvement could be hoped for from surgery.

A boy, age 14, moribund on admission, had his femur opened by gouge when he did not show signs of improvement two days after admission, and postmortem, four days later, showed metastatic abscesses of all organs. The blood culture showed *Staphylococcus aureus.*

A girl, age 11, very toxic on admission, had her tibia immediately opened by drill, and postmortem, three days later, showed purulent pericarditis, peritonitis, and multiple abscesses of the cortex of her kidneys.

A very toxic boy, age 11, with involvement of the tibia, was operated upon as an emergency (drill) and the notes state: "Postoperative temperature went up to 106° F. and did not fall after operation but went to 107° F. Delirious all during first postoperative day and unconscious the next, up to time of death."

An interesting observation regarding the temperature in the toxic patients upon whom early operation was performed, was the fact that the supposed relief of tension in the bone was but rarely followed by a drop in temperature, in many instances the tendency being rather to either show no effect, or an elevation. We regret that our statistics do not include a sufficient number of temperature recordings to warrant including them, but our observations in this respect are in accord with those of Wilensky.

A man, age 22, very toxic on admission, who had injured his femur three days previously, before operation showed a Staphylococcus blood stream infection of 15 colonies per plate. He was operated upon two days after admission, and a postmortem blood culture taken 14 hours after operation showed "innumerable Staphylococci." Incidentally, his temperature before operation was 103° F. and after operation it went to 108° F., the pulse being 100 and and 150, respectively. It is believed that this case exemplifies those instances in which the toxic patient's resistance is overwhelmed by increasing the blood stream infection.

A boy, age six, very toxic, was treated expectantly for nine days before a diagnosis of involvement of his femur was made. As soon as the condition was recognized, in spite of being acutely ill, he was operated upon and the operation notes are rather significant: "At operation, the whole thigh contained pus, coming from beneath the periosteum. The roof of the femur was removed and the patient promptly died of shock, as might have been anticipated." It is indeed unfortunate that the diagnosis of osteomyelitis was made in this instance, as otherwise he might have had an opportunity to handle his infection, as he was apparently doing.

In acute hematogenous osteomyelitis, the primary consideration is naturally to save the life of the patient and secondarily to effect a recovery as soon as possible, with a minimum of deformity, residual infection or damage to other parts of the body. It is with this thought in mind that, in the present series, we have, therefore, stressed rather those factors influencing the mortality rather than the morbidity of the condition, and from a résumé, one gathers the following impressions:

CONCLUSIONS

(1) Immediate operation with opening of the bone, whether by gouge or drill, upon diagnosis of acute osteomyelitis in an acutely toxic patient, is accompanied by an unjustified mortality, and should the patient survive it is probably in spite of, rather than because of surgery.

(2) During the acute stage rest and supportive measures alone should be adopted till the defense mechanism of the body has had time to develop.

(3) When surgery is indicated, it should be performed with as little disturbance to the part involved as is consistent with attaining its objectives.

(4) The development of secondary foci increases the mortality appreciably; when they do appear, they are more apt to do so in cases that were operated upon early rather than late.

(5) A demonstrable blood stream infection greatly increases the mortality.

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CYSTIC DISEASE OF THE SPLEEN

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IN THE American literature, reported cases of cystic disease of the spleen are quite rare. In a comprehensive article, Fowler[1] collected 86 cases of nonparasitic cystic disease, reported up to 1912. In 11 the diagnosis was made by trocar. Twenty-eight were found at postmortem. Other articles,[2, 3] in 1913 and 1924, brought the record cases up to 90. Our interest in this subject was aroused by the surgical removal by one of us of an enormous spleen containing multiple cysts, the etiology of which is somewhat obscure. Cysts of the spleen may be classified as dermoid, parasitic and nonparasitic. The spleen may contain one or two solitary large cysts or a great number of small cysts. The latter is quite rare, there being only 10 cases of this type recorded with adequate microscopic reports.

Exclusive of dermoid and parasitic types, splenic cysts are classified by Fowler[1] on an etiologic basis as follows:

I. True Cysts:
   (1) Infoliation cysts (inclusion of peritoneum, inflammatory or traumatic, small and multiple, superficial or deep [malaria and leishmaniasis]).
   (2) Dilatation cysts. Polycystic disease of the spleen. The entire parenchyma studded. Rare. Ectasia of the splenic sinuses.
   (3) Neoplastic cysts. Lymphangioma, hemangioma. Differentiation from inflammatory types may be difficult. Sarcomatous metastases.

II. Pseudocysts—Secondary:
   (1) Traumatic. Origin usually from a hematoma. Usually large and unilocular. Contents serous or hemorrhagic.
   (2) Degeneration cysts. Arising from secondary changes in infarcted areas from arterial degeneration or occlusion of blood vessels by emboli with subsequent necrosis of splenic pulp. Usually solitary and large.

Cystic disease in the spleen may present four morphologic types:
   (1) A large solitary cyst. Contents usually hemorrhagic.
   (2) Numerous very small cystic cavities, usually subcapsular or projecting from the capsule. This is the most usual type.
   (3) The so-called multiple or polycystic spleen in which the entire parenchyma is studded. Seven cases of this type are recorded: Fowler,[1] Leudet,[4] Coenen,[5] Suchanek,[6] Lubarsch,[7] Le Fort Le-

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gen,[8] Dobrzaniecki.[10] The present case makes the eighth reported.

(4) One large cystic cavity involving only part of the parenchyma, which is well preserved, with numerous small cystic satellites. (Howald,[11] Mondré,[12] Brandberg.[9])

Many published cases give no histologic details and the exact nature of the cystic disease remains obscure. The following is a selected list of reported cases of cystic disease of the spleen of the above types probably not of neoplastic, dermoid, or parasitic nature:

Leudet,[4] 1853. One cavity divided into four to five partitions by fibrous membranes lined by pavement epithelium.

Boettcher,[13] 1870. Multiple "pea-sized" serous cysts which are lined by endothelium.

Mattei,[13] 1885, male, age 68. An enlarged spleen weighing 370 Gm. Four-fifths of the splenic parenchyma was filled by a large cyst covered in part by a thin rim of splenic parenchyma. Walls were hard, cartilaginous and calcified. Surrounding this were 17 satellites varying from the size of a "hemp seed" to a "large nut."

Fink, quoted by Coenen,[5] 1890, male, age 48. Spleen enlarged and filled with numerous cystic cavities, endothelium lined.

Coenen,[5] 1910. A multilocular cyst and other numerous cysts of varied size, from "millet seed" upwards; weight 2,565 Gm. Size 33x20x10x10 cm. The spleen was removed during pregnancy. The surface was knobbed. The walls of the cyst were thin, transection revealed a honeycomb appearance, the parenchyma being riddled with numerous smooth-walled cysts of various sizes, contents clear or bloody, thin fluid. Very little normal parenchyma remained. Microscopy revealed blood and lymph sinuses of various sizes. Smaller ones unlined, the larger lined by endothelium. Coenen believed this to be a case of multiple lymphangiectasia of the spleen.

Fowler,[1] 1912, female, age 22. Abdominal trauma one year prior to the delivery of twins. Splenectomy performed following delivery because of large abdominal mass. Spleen weighed 385 Gm. Size 20x11x6 cm. A fibrous band divided the spleen into two complete parts. Entire organ was cystic, containing large and small cavities filled with jelly-like substance. Microscopy suggested dilatation of numerous lymph sinuses. Some were lined by endothelium.

Suchanek,[6] 1912. A large cystic spleen with one cyst, size of a child's head, and other smaller ones; contents clear, serous, bloody or purely hemorrhagic. Contents of varied reaction and specific gravity. No residual splenic tissue. Case described as cystic lymphangiectasia.

Bacigalupo and Grosso,[13] 1919. Multiple serous cysts in an infant found at postmortem.

Adrian Lambert,[14] 1919, female, age 34. Spleen removed at operation measuring 9x8x6 cm. Two cystic cavities communicating. Contents clear

amber fluid. "Lining smooth, shining," old thrombosed blood vessels found. Lambert believed the amyloid degeneration of blood vessels to be the etiologic agent.

Alfejew,[15] 1923. Reported cases of multiple small cysts of the spleen said to be due to dilatation of lymphatic channels. Two types were encountered:

(1) Lymphangiectasias: These appear deep in normal splenic tissues and consist solely of an alteration of the splenic tissues.
(2) Lymphangiomata: Usually dilatations distinct from normal splenic parenchyma.

Howald,[11] 1926. Collected a series of 73 cases of cystic spleens from the literature. In only 18 cases could relations with blood vessels or lymph vessels of the spleen be traced. In many cysts a distinct endothelial lining was described. In the remaining 56 these relations were absent and the cysts were unlined. In the large cysts lining cells were flat and high; in the small cysts a close formation of blood vessels was described. Howald emphasized that the delicate endothelial lining of cystic spaces might be frequently lost during manipulation, and that the lining of lymph vessels may be transformed to cuboidal epithelium. He states that adhesive cysts arise frequently from hematomata on the basis of histogenetic defects.

Mondré,[12] 1926, female, age 43. Large cystic spleen, weight 3.15 kilos. There was one large cystic cavity and numerous others "peanut to "walnut" in size. The larger cysts were buried by endothelium. In the smaller cysts epithelium was flattened to cuboidal. Splenic tissue showed pressure atrophy between the cysts.

Lubarsch,[7] 1927, female, age 41. Spleen weighed 1,320 Gm. Size 21x14x12 cm. The capsule was thick, dense and fluctuant in some areas. Section revealed about one dozen cavities, mostly rounded, size of a "walnut," and many smaller cavities, with smooth walls. Contents fluid or semisolid. Between the cavities was more solid, nodular material, dark red or grayish-yellow in color. Residual splenic tissue present only in outer layer, varying from 0.5 to 2.5 cm. in width. *Microscopic Examination:* The large cavities contained partly homogeneous and apparently filamentous network with occasional red blood cells, and fat-filled phagocytes. The walls of larger cavities consisted chiefly of hyalin delicate connective tissue, without definite lining cell layers. The smaller, more spherical cavities had a definite cell lining and homogeneous contents containing red blood cells. There were solid nodules of various sizes, gray to dark red in color. These represented cavities filled by extravasated blood and lymph material which had become organized by numerous fibroblasts and angioblasts. At the upper pole, there was splenic tissue showing similar pictures, except that in some areas the follicles were completely absent and the pulp capillaries and arteries were hyalinized and showed amyloid degeneration. In the large splenic rests were abundant and large lymph follicles with arteries partially hyalinized with amyloid. *Pathologic*

Diagnosis: "These are cystic lymphangiomata and hemangiomata, or mixtures, with organization of solid nodules by numerous blood vessels. Amyloid deposition is atypical, as is associated with a diffuse deposit of hyalin in the spleen material. Relation between hyalin and amyloid material and cyst formation is indefinite."

The case of Le Fort Legen[8] was probably of sarcomatous nature. Sections showed dense connective tissue. There were many cysts, most of which showed no epithelial lining.

Brandberg,[9] 1928. Case 1. No history. Spleen with one cyst, size of a "hazel nut," surrounded by multiple conglomerate satellites. Rest of splenic tissue normal. All cavities lined by endothelium and filled with gelatinous substance. Believed to be a case of congenital multiple lymphangiectasia, the result of ectopic lymph vessels.

Dobrzaniecki,[10] 1930, female, age 38, who suffered an acute abdominal episode, characterized by tenderness in the right upper quadrant and high temperature, following a severe trauma. One month later a large spleen was removed, measuring 25x13x14 cm. The lower portion was made up of multiple noncommunicating, large smooth-walled cysts, containing 140 cc. of yellow fluid and blood clots. Microscopically the tissue between the cysts was a homogeneous and necrotic mass containing fibrin. Blood vessels showed endothelial thickening and narrowing of the lumen. Some small vessels were obliterated. No hemosiderin was present. The author attributes the cavitation to trauma and ischemic necrosis caused by obliterative endarteritis.

Females are predisposed to the development of cystic disease of the spleen. Of 68 cases in which the sex was stated, 40 were females (Fowler[1]). This is most likely because of the periodic variations in size occurring in the spleen during the menstruation and pregnancy.[13a] During these periods the spleen may become enlarged and congested and when subjected to trauma or vascular insults, hematoma and cystic disease follow. Bircher[16] studied 54 cases of cystic spleen and attributed 17 to traumatic causes. One case was discovered during pregnancy. Subsequent operation disclosed a large cystic spleen due probably to a twisted pedicle, the result of trauma. The cystic tumor may increase in size following delivery, and necrosis frequently occurs (Routier-Wells[13]). Coenen[5] removed a polycystic spleen during pregnancy. Dowd[17] incised a large cystic spleen postpartum. There was a history of trauma. The walls were necrotic: "almost the entire spleen came away in sloughs." Trauma is a very important factor. In many cases, cystic spleens have apparently resulted from abdominal blows delivered as long as ten years prior to the operation. Eventually, infarction, hemorrhage and cyst formation, usually of the solitary type, occurs. Case 2 of Hamilton and Boyer[18] apparently resulted from an abdominal blow delivered four years prior to removal of a spleen measuring 15x15x8 cm. containing a large solitary hemorrhagic cyst. Traumatic hemorrhagic cysts may contain as much as ten liters of fluid.[1] On the other hand, enormous cysts of the spleen may develop without a history of trauma, as in our case and that of Gosselin.[19] In the

latter, a spleen containing a collapsed cyst the size of a "football," and containing three liters of fluid, was removed from a middle-aged female. There was a partial obliteration of the splenic artery.

Nineteen of Fowler's[1] series of 44 cases probably were of traumatic origin—five from disintegration (infection and arterial degeneration), eight were cysts into which secondary hemorrhage had occurred, two were neoplastic. Usually the single, large, unilocular cyst originates secondary to intraparenchymal or subcapsular hemorrhages. Later the cellular contents are deposited upon the lining wall and the fluid eventually becomes serous and clear. Possibly many unilocular solitary cysts originate from fusion of smaller cavities. Often trabeculated projections into cyst cavities are suggestive of multiple, broken-down septa. Even many small cysts are multilocular at onset, although they appear single. The cyst wall is usually thin and often formed by only a very thin capsule.

The huge spleens of malarial and syphilitic patients are likely to be injured by hematoma and cyst formation. Perisplenic adhesions are prone to occur in hyperplastic spleens. Perisplenitis and cyst formation are apparently related. Hemorrhagic cysts occur in Arabs, due to ruptures restricted by adhesions.[1] In typhoid fever, rupture of a distended capsule might possibly result in cyst formation. Numerous small multiple surface cysts in malarial splenomegaly are described (Subbotic[13]). This author attributes the surface cysts to rupture of the splenic capsule over the distended pulp. Cystic spleens occur in pemphigus (Bednor[13]) and mumps (Fereral[13]) and in syphilis (Harnett[13]). The latter is due to endarteritis with rupture of intrasplenic blood vessels.

Boettcher[13] states that small, deep, multiple cysts originate secondarily to amyloid changes in the blood vessels and cystic degeneration following splenic necrosis. Walls of these cysts may be of connective tissue if organization has taken place. Contents vary with age of cyst. Hematoidin and cholesterol crystals usually present in old cysts. Multiple cysts may be small or superficial or deep. Contents of old subcapsular hematomata may be gradually transformed into clear serous fluid.

Beneke[13] believes that small, multiple surface cysts originate from infoliation of peritoneal endothelium carried deep into the parenchyma when the splenic capsule is ruptured due to trauma. Small capsular tears permit fragments of splenic tissue to protrude; later these become sealed off and subsequently form cyst cavities. He states that cells lining these cysts and the peritoneal endothelium are identical.

Renggli[13] describes cysts lined with cuboidal epithelium and explains the presence of multiple deep cysts by a similar theory. Due to superficial inflammatory processes, portions of peritoneal endothelium are snared off which eventually are carried into the splenic substance and later, when stimulated to growth, form cysts lying deep in the parenchyma. A single layer of cuboidal epithelium lining these cysts is similar to that of the peritoneum, except that the latter is somewhat flatter due to pressure of neighboring or-

gans. He states that these cysts originate in the embryo, where the endothelium of the peritoneum shows its original cuboidal character. Otto[13] believes that this explanation holds only for small superficial cysts with a flat layer of cells not surrounded by splenic tissue.

Pepere[13] points out that cellular nests may persist in the splenic capsule because of deviation of portions of the perisplenium during embryonic life. Failure of these residues to disappear gives rise to serous cysts.

Case Report.—R. Z., white, female, age 46, housewife, was first observed December 4, 1937. The patient had experienced a sensation of a "lump in chest," during the past three years, gradually increasing in intensity until the present time. Recently she experienced dyspnea without exertion and noticed that her abdomen was protuberant. Six months ago she felt a painless mass in the left upper quadrant of her abdomen. No loss of weight, appetite good, no dyspepsia. Appendix and one ovary removed 11 years previously. Hemorrhoidectomy and vaginal plastic seven years ago. Menses always regular until six months ago when she had three periods in July, she skipped August, and resumed normalcy again in September. No history of trauma could be obtained.

Physical Examination revealed a well nourished female, not acutely or chronically ill, no cyanosis or dyspnea. Abdomen protuberant, with inversion of umbilicus. Distended epigastric and lateral thoracic veins. Flanks were resonant with dullness over a large mass, the size of a volley-ball, which was visible on inspection of left upper quadrant. The tumor felt nodular and cystic and could be separated from the costal margin. It did not move on palpation. Extremities showed no large veins or edema. Vaginal examination revealed no significant findings. Hb. 9.5 Gm., 58 per cent; R.B.C. 3,300,000; W.B.C. 7,100. Differential count showed no significant changes. Wassermann reaction was negative.

Operation.—December 8, 1937: A ten-inch, left midrectus incision revealed an enormous mass, evidently the spleen, occupying the entire upper half of the abdomen and extending down below the umbilicus. The peritoneal surface of the tumor was adherent to the entire dome of the diaphragm and to the posterior parietal peritoneum. Although the adhesions were thick, they were easily separated and the spleen delivered from the abdominal cavity. Adhesions to the sigmoid, pancreas and the splenic pedicle were doubly clamped, cut and ligated. Recovery was uneventful. The patient remained in the hospital 22 days.

Follow-Up.—January 12, 1938, six weeks postoperative: General condition excellent, no masses palpable, liver not palpable and the operative wound is healed solidly throughout. Blood count: R.B.C. 4,200,000; W.B.C. 8,300, Hb. 70 per cent. June 21, 1938: Condition excellent; no loss of weight, no palpable masses in the abdomen. Blood count: R.B.C. 4,100,000; W.B.C. 8,700; Hb. 70 per cent.

Pathologic Examination.—Dr. Chester R. Brown: Specimen consists of an enormous spleen weighing 1,500 Gm., measuring 28.7x20x12.5 cm. The spleen has been removed close to the entrance of the splenic artery and vein into the hilus. There is no evidence of thrombi within these vessels. Capsule is considerably thickened and in some areas is covered by dense, white patches firmly adherent to the underlying parenchyma. Sagittal section reveals a very unusual appearance. The spleen is surrounded, on one side, by a narrow border of apparently uninvolved parenchyma 4 cm. in thickness, resembling normal splenic tissue. This residual parenchyma consists of an admixture of solid tissue and cystic spaces. The solid part is composed of numerous larger and smaller areas of friable tissue, yellow to brown in color, more or less completely surrounded by thin fibrous septa. These masses vary in size from 1 to 2 cm. to large nodular masses 8 to 10 cm. in diameter. There are four cystic areas varying in size and quite irregular in shape. The two smaller areas are 6 to 12 cm. in diameter and another, completely cystic, approximately 7.5 cm. in diameter. No distinct membrane lines these cavities. Instead, irregular,

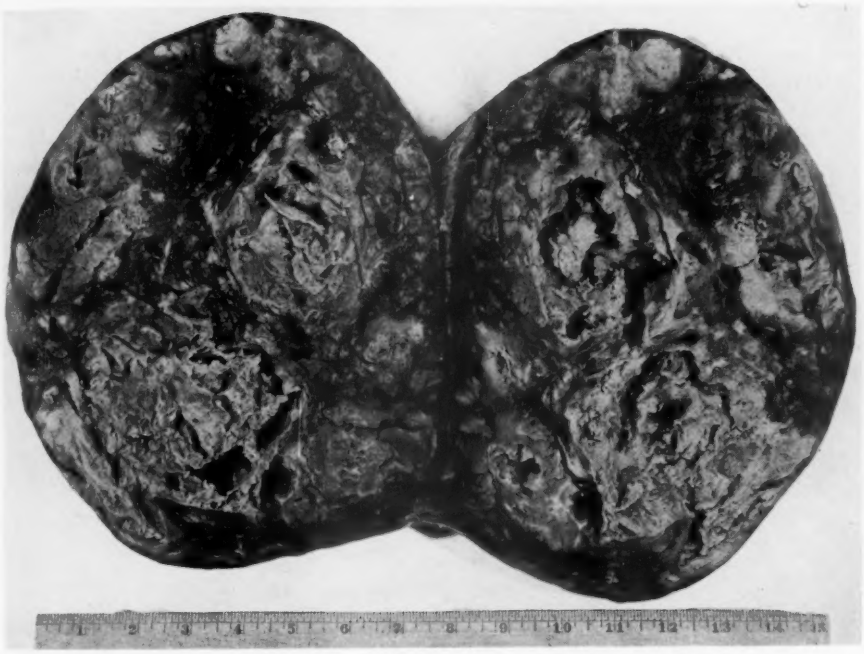

FIG. 1.—Photograph of the gross specimen. Note solid areas (dark) and various stages of cystic degeneration (light).

friable, nodular masses project into the lumen of the cysts from all sides, suggesting that the cavities had been formed by disintegration of parenchyma, previously solid (Fig. 1).

Microsopic Examination.—Sections of the capsule and pulp were stained with hematoxylin and eosin, mucicarmine, Mallory's phosphotungstic acid hematoxylin, Mallory's

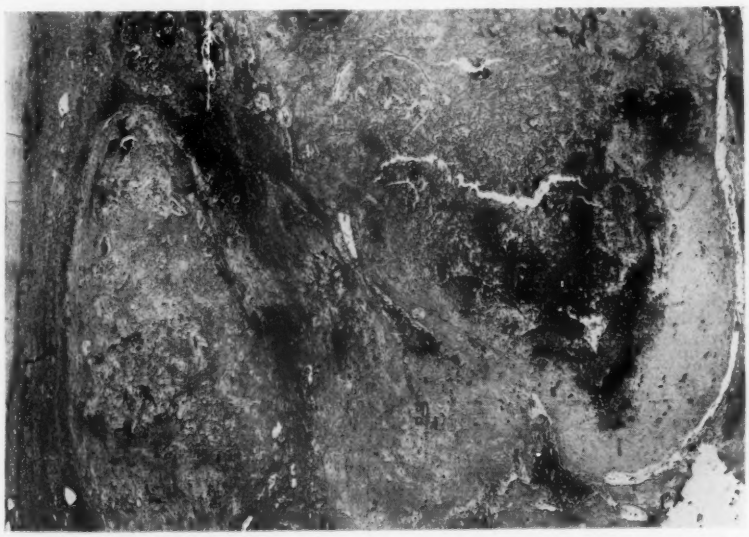

FIG. 2.—Photomicrograph of spleen taken near surface. At the left is residual parenchyma, showing dilated lymph channels. The remainder of the pulp is entirely necrotic. (Low power)

aniline blue and potassium ferrocyanide. A section taken near the thickened capsule shows this to be composed of dense collagen fibrils. Immediately beneath this is a thin layer of residual splenic tissue, evidently the only remaining tissue which can be definitely recognized as a part of splenic pulp. This layer contains a few atrophic follicles, reticulum cells and fibrocytes with thickened trabeculae and a few dilated channels lined by a single layer of flat cells. Splenic sinuses are partially filled with red cells. Abundant collagen fibers lie within the thickened capsule and trabeculae and are condensed about the cystic areas forming more or less of a capsule. Beneath this layer, necrosis and cystic degeneration begin. Large areas of faintly pink-staining acellular material resembling coagulated

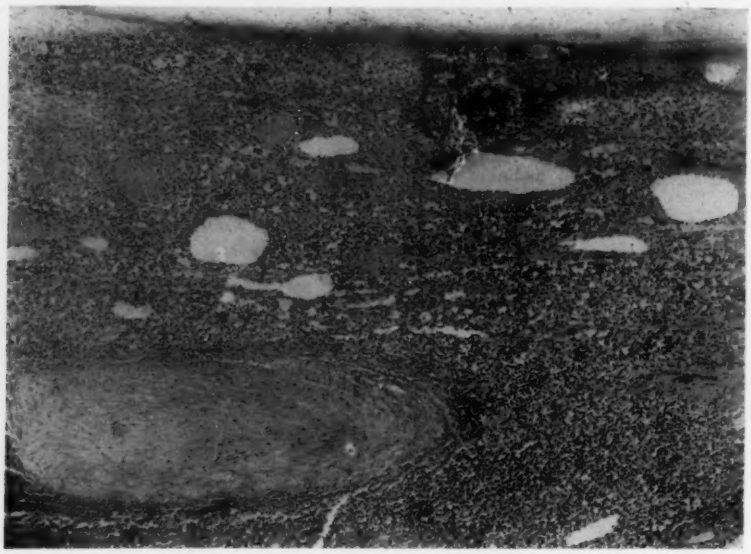

FIG. 3.—Photomicrograph of residual parenchyma near cortex showing dilated lymph channels and compressed atrophic pulp. (Low power)

serum and, in some areas, coagulated fibrin alternate with large extravasations of red cells not definitely in sinusoids. No endothelial lining is evident on the wall or within cystic spaces. Inflammatory cells are very rare. Portions of thickened trabeculae show dark-staining areas arranged in fibrillary strands. These give a positive iron reaction. Within the trabeculae are a few large congested blood vessels which show no thromboses, necrosis or amyloid degeneration. Mucicarmine stain failed to reveal the presence of mucus. *Pathologic Diagnosis:* Multiple cystic disease of the spleen.

SUMMARY

The case history and pathologic details are given concerning an enormous cystic spleen which had apparently developed without evidence of abdominal trauma.

A short summary of the pertinent literature is included.

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RHABDOMYOSARCOMA OF THE URINARY BLADDER

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RHABDOMYOSARCOMA arising from the musculature of the bladder is rarely seen. However, because of its grave prognosis and the difficulties encountered in treating it, this neoplasm is of special interest. The first case of malignant rhabdomyoma of the urinary bladder was that described by Mönckeberg,[25] in 1907, occurring in a female, age 23. The tumor was resected, but recurred promptly and the patient died several months later. There were no metastases apparent. Another case was observed, in 1929, by Houette,[14] in a congenital diverticulum of the bladder in an infant, age 13 months. Montserrat and Garcia[26] reported a case in a male, age 43, in 1933. Partial resection of the bladder was performed but the patient died four months later; autopsy was not obtained. In 1936, Welfeld, Hill and Hillebrand[42] reported two cases in infants, both of whom died soon after treatment, with extensive local recurrence but no distant metastases. The only case of urinary bladder rhabdomysarcoma with distant metastases was reported by Mackenzie and Chase,[23] in 1928, in a female, age 69. Autopsy showed a direct extension of the vesical neoplasm to the left ureter and distant metastases to the portal lymph nodes, liver and duodenum.

As far as we can ascertain from our search of the literature, the present case report constitutes the seventh instance of vesical rhabdomyosarcoma reported, and the fourth case to be observed in infants.

The histologically benign variant of this striated muscle tumor, the rhabdomyoma, has also been observed in the urinary bladder. The first case of this type was that of Cattani,[3] in a boy, age 12, reported in 1884. Vincenti,[41] Pavone[29] and Huesler[15] each added one case to the literature. Their patients were 13, 22 and seven years of age, respectively. In 1903, Benenati[2] assembled a group of 65 cases of rhabdomyoma, three of which occurred in the bladder. Shattock[36] described four specimens of this tumor from the Museum of the Royal College of Surgeons, in 1909. These all occurred in infants under two years of age. In 1924, Deming[6] reported a case of a histologically benign rhabdomyoma of the bladder in a 21 month old infant. This constitutes a total of 12 recorded cases of benign rhabdomyoma of the urinary bladder.

Because of the normal abundance of smooth muscle fibers in the muscular layers of the bladder wall, one might expect to find the leiomyoma and leioymo-

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sarcoma more frequently than the striated muscle tumor. Keene and Tompkins[18] collected from the literature 59 cases of benign leiomyoma of the bladder. Three cases of leiomyosarcoma of the urinary bladder have been reported; none of these exhibited distant metastases. The cases of Powell[30] and Krauskopf[19] occurred in elderly individuals. The case observed by Caylor and Walters[4] occurred in a four year old boy who died within two months following resection and irradiation of the bladder.

Pathogenesis.—There are a number of theories concerning the pathogenesis of striated muscle tumors of the urinary bladder. Striated muscle fibers are found normally in the fetus, child and adult, around and often within the substance of the anterior part of the prostate, constituting the external vesical sphincter. A more tenable hypothesis is the derivation of these tumors from cells of the myotome (anlage of the striated muscle of the abdominal wall) which have become displaced during the caudal growth of the wolffian duct to its vesico-urethral destination.

Pathology.—Grossly, the rhabdomyosarcomata of the bladder do not differ from the numerous other types of mesoblastic vesical tumors. The growth frequently occurs in the form of grape-like masses suggesting hydatidiform mole. Hence the descriptive name, sarcoma botryoides, applied to the rhabdomyoma of the cervix. Usually, the tumor is of a white to grayish-yellow color, and has a fleshy consistency. The surface is usually smooth and translucent. Occasionally, glairy fluid can be expressed from the tissues on gentle pressure. Usually, there is no ulceration of the bladder mucosa as the growth originates in the submucosa or intermuscular substance. The space of Retzius is rapidly invaded, and following cystotomy or resection, the tumor usually grows luxuriantly to the abdominal wall, as happened in the present instance. Distant metastases are rare, as has been pointed out.

Histologically, the characteristic finding is a mesoblastic tissue composed predominantly of large cells with eosinophilic cytoplasm, containing longitudinal and transverse fibrillae. These cells contain one to many large, oval, vesicular nuclei with deeply stained nucleoli. The cells vary markedly in shape, size and staining quality, and mitotic figures are frequent.

Clinical Features.—The symptoms associated with the presence of this tumor are quite variable, but are not different from those of vesical sarcomata in general. Occasionally, there are no associated genito-urinary symptoms, the only complaints being abdominal pain or the consciousness of an abdominal tumor. Hematuria is rare, particularly as an initial symptom. Descalopoulos,[8] in 1929, found hematuria as a symptom in only four out of 20 cases of bladder sarcoma in infants. Due to the infiltration of the bladder neck and loss of bladder contractility, acute or partial retention of urine is a frequent occurrence. Hence, the commonly associated symptoms of dribbling, enuresis, frequency, incomplete emptying of the bladder and dysuria. The diagnosis is frequently made accidentally at exploratory operation for an abdominal tumor of undetermined nature. In most of the reported cases of bladder sarcoma,

diagnosis has creditably been established before operation by cystoscopy or cystogram.

Prognosis.—The prognosis associated with rhabdomyosarcoma of the bladder is grave, as it is for all vesical sarcomata. None of the reported cases of rhabdomyosarcoma of the bladder have survived for more than a year following operative intervention. Most of the cases were treated by either cystotomy alone, cystotomy with partial resection of the bladder, sometimes followed by postoperative radiation, or cystotomy with cautery-fulguration of the tumor. The postoperative radiation administered has been in the form of roentgenotherapy, surface or interstitial application of radium element or radon. In our case, telecurietherapy with the four gram radium bomb was employed. The results have been uniformly bad. Rhabdomyosarcomata are usually radioresistant, as are most tumors in which an attempt is made to form a differentiated organ. Munwes[27] is the only author to present at all encouraging results in the treatment of vesical sarcoma. Three of his cases have remained well over five years, following radical operative treatment. In view of the fact that rhabdomyosarcomata rarely produce distant metastases, and that death usually occurs from cachexia and inanition associated with the exuberant growth of the local recurrence following incomplete surgical eradication of the disease, one is inclined to agree with Mintz,[24] who advocates total cystectomy, including resection of the urethra. In consideration of the definite, though slight and temporary, response to radiation observed in our case, telecurietherapy appears worthy of trial in advanced, inoperable cases.

Case Report.—A. N., male, age 10 months, was admitted to the Michael Reese Hospital, December 28, 1937. The child had been well until two months previously, at which time it commenced having severe pain on urination, as evidenced by an agonized facial expression and compression of the lower abdomen with its hands during attempts at micturition. Suprapubic cystotomy was performed elsewhere, and the parents were informed that the child was suffering from a malignant tumor of the bladder. Within one week following operation, a fungating mass had grown out to the anterior abdominal wall at the site of the cystotomy.

Physical Examination.—The patient was markedly emaciated. The head exhibited a moderate hydrocephalus; the contour was brachycephalic, and a prominent ridge was palpable at the temporoparietal suture. The anterior fontanelle was widely patent. The skin of the back, chest and thighs was studded with café-au-lait spots. No skin tumors were visible. The suprapubic region presented a fungating mass, 12x6 cm. in size, at the site of the previous suprapubic incision (Fig. 1). Urine seeped constantly over the surface of this tumor. For the most part it was pink in color but in places was covered by a greenish-gray necrotic membrane. Biopsy suggested a malignant mesoblastic tumor apparently of neurogenic origin. Roentgenograms of the chest, skull and long bones showed no evidence of metastasis.

Treatment.—Palliative treatment in the form of external radiation was instituted, and 1,000 mg.-hr. was administered daily on the four gram radium bomb at 10 cm. distance, until 14,000 mg.-hr. had been given. The tumor diminished slightly in size during this two weeks' course of therapy, but the child had become so emaciated (its weight having dropped from 16 pounds, four ounces to ten pounds, twelve ounces) that radiation had

to be discontinued. Its general condition grew steadily worse; the tumor increased again in size; and the child died, four weeks after treatment had been stopped.

Autopsy.—There was a marked external hydrocephalus. The skin of the back, chest and thighs presented many café-au-lait spots varying in size from 0.5 to 2 cm. in diameter. The suprapubic region of the abdominal wall was covered by a fungating, pinkish-gray mass 15x12x6 cm. in its greatest dimensions. The surface of the tumor was moist and granular. On cutting through the abdominal wall one found that the tumor arose from the outer coats of the bladder wall. The space of Retzius was completely filled by tumor. The mucosa was smooth and apparently not involved. Both ureters were moderately dilated.

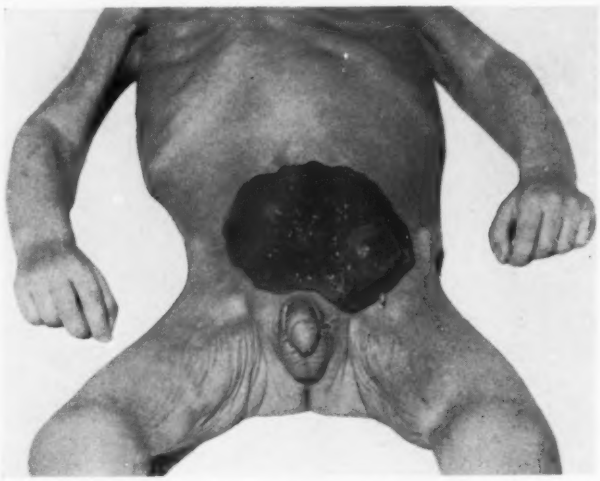

FIG. 1.—Showing the rhabdomyosarcoma of the urinary bladder with extension to abdominal wall.

Pathologic Examination.—In a section of the bladder wall near the mucosa, a few alveolar-like structures were seen to lie in a dense stroma and were composed of transitional epithelial cells isolated from the surrounding tissue by a well formed basement membrane. The stroma was cellular and contained various types of cells. Many of the nuclei were oval in form and appeared to have no surrounding cytoplasm. Others, and this type predominated, consisted of elongated dark-staining nuclei from whose poles fibers were seen to emanate. In another area, large nuclei were arranged in circular form surrounded by pink-staining material. Occasionally, large fibers with peripherally placed nuclei were seen. Cross and longitudinal striations were noted in fibers which were quite variable in size. A moderate number of mitotic figures were seen throughout the section. *Histologic Diagnosis:* Rhabdomyosarcoma of the urinary bladder.

COMMENT.—This was a malignant, striated muscle cell tumor arising from the wall of the urinary bladder in a male infant, age 10 months, which extended to the abdominal wall following cystotomy and in a short time attained the size indicated in Figure 1. Because of the emaciated condition of the child, the extensiveness of the bladder tumor, and the possibility of a tuberous sclerosis associated with the pigmentation suggesting von Recklinghausen's disease (neither being found at autopsy), operation was deemed inadvisable. Palliative radiation was administered by telecurietherapy (radium bomb) with the result that the tumor began to react locally and shrink

in size. Because of the marked weight loss which occurred, such radiotherapy had to be discontinued after two weeks.

At autopsy, the only findings of significance, besides the bladder tumor, were the café-au-lait spots and the external hydrocephalus. The authors wish to call attention to the frequent association of café-au-lait spots (as observed in this and other recent cases) with tuberous sclerosis, glioma of the brain and benign or malignant mesothelial tumors, including those of the genito-urinary tract.

Discussion.—In connection with our study of the striated muscle cell neoplasms of the urinary bladder, it appeared of interest to investigate the occurrence of such tumors in other parts of the body. The earliest record of a striated muscle tumor is apparently the case of Rokitansky,[33] reported in 1849.

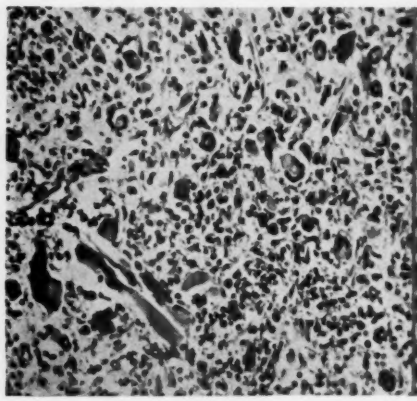

FIG. 2.—Photomicrograph of the rhabdomyosarcoma of the urinary bladder; a few fibers with longitudinal and cross striations are to be seen.

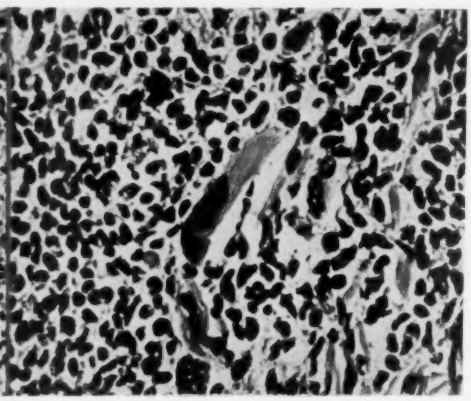

FIG. 3.—Photomicrograph of the rhabdomyosarcoma of the urinary bladder. (High power)

This was a paratesticular tumor, in a boy, age 18, composed of striated muscle and presumably arising from the gubernaculum testis. Benenati,[2] in 1903, collected 65 cases of rhabdomyoma. Over one-half of these were located in various portions of the genito-urinary tract. Most of these cases occurred in the first or second decade of life. Only one of Benenati's cases exhibited malignant characteristics histologically or clinically. This case was a tumor arising from the muscles of the thigh with widespread metastases.

Malignant rhabdomyoblastomata occur in the skeletal musculature somewhat more frequently than in the genito-urinary system. Charache,[5] in 1936, collected 11 cases from the literature. In most of these, the tumor followed severe trauma, in contrast to the genito-urinary rhabdomyoblastoma which is usually thought to be the product of disturbed embryologic development. These tumors occurred in older individuals and metastasized more frequently than the genito-urinary tumors of similar histologic nature. Charache's case exhibited metastases to lungs, liver, kidneys and local lymph nodes. Rakov[31] has recently written a most comprehensive summary of this condition, which was diagnosed in 15 cases at the Oncological Institute in Leningrad.

This variety of tumor is encountered even more frequently in the cardiac musculature. Reeves and Michael[32] mentioned the existence of 45 cases of rhabdomyoma of the heart and reported an additional case of their own. The condition is especially prone to occur in infants with cerebral sclerosis. Of 12 cases of cerebral sclerosis observed by Wolbach,[43] six had rhabdomyoma or rhabdomyosarcoma of the heart.

Both benign and malignant varieties of this striated muscle neoplasm have been found throughout the genito-urinary tract. According to Bell,[1] leiomyomata, rhabdomyomata, fibromata and neurofibromata are not infrequently encountered in association with tuberous sclerosis. On the other hand, Kass[16] maintains that there are but five authentic cases of neurofibromatosis of the bladder in association with von Recklinghausen's disease, and that his case constitutes the only reported case of this condition occurring in childhood.

While the so-called Wilms' tumor of the kidney is usually an adenosarcoma histologically, it not infrequently shows foci of adult or undifferentiated embryonal striated muscle and at times is a pure rhabdomyosarcoma.

Some ten cases of rhabdomyosarcoma of the prostate have been reported. Greig's[11] case and that of Katzmann[17] occurred in early childhood. The cases of Ewing,[9] DeRom and Thomas,[7] Kretschmer[20] and of Foucar[10] were all in young adults. Metastases were observed only in the cases of Squier[38] and Foucar.

The literature on rhabdomyosarcoma of the testis is somewhat confusing, because of a tendency to classify as rhabdomyosarcomata tumors which are actually teratomata containing foci of striated muscle. Most of the pure striated muscle cell tumors of the testis have occurred in children or young adults. Neumann's[28] case was a rhabdomyoma in a child, age 3½ years. Schamschin's[34] case was the malignant variant of this neoplasm and occurred in a child, age 4. Ssinelscikowa[39] reported a case in a boy, age 15, with mediastinal, pulmonary and diffuse intra-abdominal metastases. One of us (Uhlmann) has personally observed a case of rhabdomyosarcoma of the testis in a male, age 22, who exhibited retroperitoneal lymph node metastases at death, which occurred two years after the onset of the condition. Rhabdomyosarcoma of the spermatic cord has been observed in young males by Hirsch,[12] Mönckeberg[25] and Stoercke,[40] the latter's case being accompanied by diffuse metastases.

Sporadic cases of rhabdomyosarcoma of the corpus uteri have been found in elderly women by Lochrane,[21] Shaw[37] and Shapiro.[35] The occurrence of striated muscle tumors in the uterus is difficult to explain. It has been suggested that the displacement of embryonic mesodermal cells from the myotome of the dorsal region must occur during the caudal growth of the wolffian duct toward its vesico-urethral anlage. This would account for the occurrence of striated muscle cell neoplasms not only in the uterus, but in the cervix and vagina as well.

The vulvar orifice in children is apparently one of the more common locations for this neoplasm. Holmes,[13] in 1906, compiled 39 cases of rhabdo-

myosarcoma of the vulva, and several cases have been reported since. Lockwood's[22] case developed generalized intra-abdominal metastases.

SUMMARY AND CONCLUSIONS

In conjunction with the report of a personally observed case of rhabdomyosarcoma of the urinary bladder in an infant, age 10 months, the authors have reviewed the pathogenesis, clinical features, histologic characteristics and prognosis of this rarely observed tumor.

The occurrence of benign rhabdomyoma of the bladder is mentioned, and the frequency of rhabdomyosarcomata in other organs of the body is reviewed.

Total cystectomy, including resection of the urethra, is recommended as the treatment of choice in operable cases. In advanced cases, telecurietherapy appears worthy of trial, especially since distant metastases are rarely observed in this condition.

The authors wish to thank Dr. Otto Saphir, Pathologist of the Michael Reese Hospital, for his interpretation of the histologic sections.

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FURTHER OBSERVATIONS ON BENIGN TUMORS OF THE TENDON SHEATH

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FURTHER observations as to the histogenesis of benign tumors of the tendon sheath and the opportunity of investigating 23 more cases of such tumors led us to make this report.

From a review of the recent literature, it appears that the question of whether this type of tumor is a true neoplasm or merely a granuloma is still a matter of much dispute. Sprenger[1] considers the tumors of the tendon sheath as xanthomatous giant cell granulomata, since he believes them to be traumatically conditioned, chronically inflamed resorptive tumors. Lecene and Moulonguet[2] do not include these tumors among the neoplasms, showing their dystrophic origin. Berti[3] states that the tendon sheath tumors are pure and simple granulomata, obscure with respect to their etiology and pathogenesis, but sufficiently clear to permit their classification as previously mentioned. In the opinion of Bloodgood,[4] they are real granulation tissue and often of the xanthoma type.

On the other hand, Gorog,[5] Torchiana,[6] Durante,[7] Tomiselli,[8] Katsurashima,[9] Spiess,[10] King,[11] Faulkner,[12] Beckman,[13] Albertini,[14] Mathews,[15] Cooperman,[16] Aguilar,[17] Vermooten,[18] Bellamy,[19] Krogins,[20] Lewis,[21] and Geschickter and Lewis[22] consider these tumors to be true neoplasms. Although the terminology differ with the various authors, the terms xanthosarcoma, myeloplax tumors, giant cell sarcoma, myeloid endotheliomata, and myeloxanthomata are being used.

Authors who regard these tumors as neoplasms do not consider the presence of blood and cholesterol as primary but as a secondary factor, since these tumors are, due to their position in growth, easily subject to trauma.

Material Considered.—We have clinical data on 14 of 23 cases, have summarized the clinical course in Table I. The specimens of the other nine cases were sent in to the laboratory from the outside, without any accompanying clinical data.

Age Incidence and Site of Tumor.—The tumors occurred in individuals between the ages of eight and 70, all but five patients being between the third and fifth decade of life. In 11 cases, the tumors were situated on the hand, eight cases having them on the right hand, involving the index finger in two; the third finger in four; and the fourth finger in two instances. Three cases were located on the left hand. In two instances the tumor was

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TABLE I

SUMMARY OF 14 CASES OF BENIGN GIANT CELL TUMORS OF THE TENDON SHEATHS

No.	Age	Sex	Race	Location	Recurrences	Size in Cm.	History of Trauma	Duration	Comment
1	40	F.	C.	Prox. phal. rt. ring finger	0	1.0 x 0.7 x 0.9	No	12 mos.	—
2	9	F.	C.	Second phal. rt. third finger	0	0.5 x 0.7 x 0.4	No	12 mos.	Pain on pressure
3	31	F.	W.	Rt. index finger	1	1.5 x 1.5 x 0.8	No	24 mos.	Pain occasionally
4	70	M.	W.	Rt. ankle	0	2.5 x 1.8 x 2.5	Yes	18 mos.	Pain occasionally
5	13	M.	C.	Second phal. rt. third finger	0	2.0 x 2.0 x 1.0	No	18 mos.	—
6	13	M.	W.	Rt. lat. bord. sole rt. foot	1	1.5 x 1.5 x 1.0	No	24 mos.	—
7	46	F.	C.	Second phal. rt. third finger	0	3.5 x 7.3 x 1.5	No	48 mos.	—
8	30	F.	W.	Radial side rt. ring finger	0	1.3 x 1.0 x 0.6	No	12 mos.	—
9	45	M.	W.	Rt. palmar surface opposite third finger at metacarpal phalangeal joint	0	1.3 x 1.3 x 0.5	Yes	9 mos.	Pain in palm
10	8	F.	W.	Second phal. rt. index finger	0	1.5 x 1.5 x 0.8	No	14 mos.	Pain on pressure
11	28	F.	W.	Second phal. L. fifth finger	0	1.2 x 0.9 x 1.5	Yes	24 mos.	Pain on pressure
12	50	F.	W.	Prox. phal. l. ring finger	0	1.2 x 1.2 x 0.7	—	—	—
13	—	M.	W.	Back of neck at sixth cerv. vertebra	2	5.5 x 3.7 x 3.5	No	6 mos. 36 mos.	—
14	—	M.	—	L. ring finger	0	—	—	—	—

Cases Nos. 15 to 23, inclusive, had no accompanying clinical data.

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situated on the fourth finger, and in one instance on the fifth finger. In the remaining three cases, one tumor was found on the back of the neck at the level of the sixth cervical vertebra and evidently arising from the aponeurotic sheath of some of the deep muscles of the back. The second arose from the fascial sheaths about the ankle, and the third arose from the lateral border of the sole of the right foot.

Duration.—The duration of time between the detection of the growth and the administration of medical attention varied from nine months to four years, and in one case pain was present for three weeks before the patient sought medical aid. Only three cases gave a history of trauma; one occurred 14 months, the second 18 months, and the third two weeks before the tumor growth was apparent to the patient.

Incidence of Recurrence.—Recurrence occurred in three cases; the tumor in the first case returning about five months after operation, the second, five years after the first and one year after the second operation, and the third, 10 years after the first operation.

Sex.—Ten of the 23 cases mentioned were females and eight males. Unfortunately, there are no clinical data available on the remaining five cases.

Pathologic Examination.—Gross: The size of the tumors was determined in 13 cases, the largest being that of the neck, measuring 5.5 x 3.7 x 3.5 cm., and the smallest being that of the second phalanx of the right third finger, measuring 0.5 x 0.7 x 0.4 cm. The tumors were found to be firm, lobulated, and cauliflower-like in appearance, and having numerous fibrous tags. The sectioned surfaces were grayish-white in color and streaked with areas of darker gray. Some areas of these tumors were tinged canary-yellow to yellowish-brown.

Microscopically, all the tumors stained with hemalum and eosin were found to contain type cells which were characterized by their polygonal or oval shape. The nuclei were of moderate size, round, oval, or slightly elongated, frequently somewhat indented, and with fine or occasionally coarse granules of chromatin. The cytoplasm was sparse. The type cells which tended to line the crevices contained a little more cytoplasm, except in two cases, where the desmoplastic change was so marked that the cells were elongated and had protoplasmic processes with a suggestion of fine fibrils extending from the cellular membranes. The nuclei here were also elongated and had coarse chromatin granules scattered throughout. With the exception of one, all the tumors had cleft formations, and in that one exception, there was a suggestion of the clefts. In areas where the type cells were separated from each other by connective tissue, it was found that the nuclei were elongated and had no apparent cytoplasmic membrane. In some of the tumors, and especially in that situated on the neck, there was definite evidence of transition of the type cell from the polygonal shape to the fibroblastic type.

Giant cells were found to be present in every case. They were characterized by being fairly well defined and containing a homogeneous and slightly eosinophilic stained cytoplasm, with nuclei which numbered five to 50, and

in two cases, where the cellular elements were quite proliferative, 50 to 100 nuclei were found per cell. These nuclei were regular, slightly oval or round, and had a fine, deeply stained chromatin network. Many of these giant cells were found in the crevices lined by the type cell.

Iron pigment, xanthoma cells and histiocytes laden with iron pigment were found in only seven cases of this series. These elements were found to be closely related. The xanthoma cells, the iron pigment, and the pigment-laden histiocytes were usually situated near a blood vessel, indicating that at one time hemorrhage occurred, and with the disintegration of the red blood corpuscles, the hemosiderin and cholesterol deposits were invaded by the histiocytic elements of the body. In five tumors, the capsule was partly formed by a thick layer of xanthoma cells in which iron pigment was found. In six instances of the above seven cases, giant cells were found close to the iron pigment, and they were characterized by peripherally placed, round, pale-stained nuclei with a pale-stained cytoplasm closely resembling the foreign body giant cell.

All of the tumors had capsules of loose to dense connective tissue which projected into the tumor mass and split up, as it went along, into fine coarse fibrillar strands which acted as a supporting network for the type cells. Hyalinization of the connective tissue was found in some instances, especially towards the center of the tumor tissue.

The blood vessels in the tumor masses were few and thin-walled. The endothelium was flattened. In the capsule of the tumors, however, some of the vessels had thickened walls, and the endothelium was swollen.

Discussion.—In view of the present study of these cases, and comparing them with the various theories offered on the histogenesis of benign tumors of the tendon sheath, we are more inclined to consider these tumors as true neoplasms and of mesothelial origin, for the following reasons: Throughout this entire series of cases, there are type cells which are characterized by round, oval, polygonal, or at times elongated shapes, with a somewhat distinct and slightly eosinophilic cytoplasm and containing a round, oval or slightly elongated nucleus which is often indented. These cells, in every case but one, which offers but a faint suggestion, show a definite tendency to line clefts which, in a way, imitate the arrangement of synovial cells in a normal tendon sheath surrounding a tendon (Fig. 1). King[11] stresses the fact that synovial membranes have a characteristically histologic picture, and that tendon sheath tumors may be interpreted in terms of this normal cellular structure. This impressed him with the fact that the synovial spaces in tumor tissue and not the giant cells or xanthoma cells are an important and characteristic feature of this tumor. He concludes, therefore, that tumors of tendon sheaths arise from the cells of the synovial membrane of the sheath, and the morphology and nature of the growth depend upon the potentialities of the originating cells.

In other instances, where the type cell is individually separated by connective tissue, the cells are found to be elongated, frequently have apparent

protoplasmic projections of the cytoplasm, and occasionally fibrils. The nuclei are elongated with fine chromatin network. This is especially noted

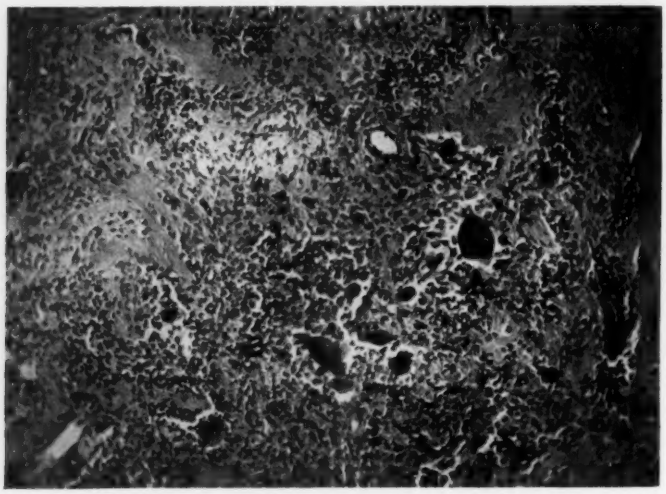

FIG. 1.—Photomicrograph illustrating the giant cell (A), and the crevices (B). These crevices may be considered as cracks in the tissue but are not so, since they are seen persistently in all tumors of this type and are quite regular in shape and are always lined by a single row of epithelial-like cells. (×150)

in three of our cases. In two cases, there was active proliferation and a few mitotic figures were found, the tumor cells as a whole took on the appearance of proliferating fibroblasts with elongated nuclei containing nucleoli

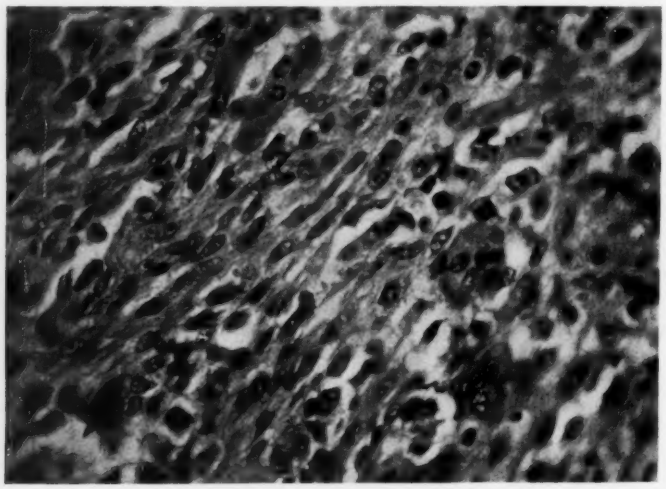

FIG. 2.—Photomicrograph illustrating the tendency of the type cell to become fusiform and fibroblastic in nature. (×600)

(Fig. 2). In two cases, particularly that of the tumor on the back of the neck, the type cell seemed to show transitional forms taking on the appearance of the swollen, elongated, fibrillar, connective tissue cell with a swollen

and elongated to oval nucleus. In the more dense portions of the connective tissue of this tumor, the cells became elongated and showed formations of extracellular fibrillar connective tissue. The above described finding may be a factor in the great amount of connective tissue usually found in these tumors.

This is substantiated by Vaubel,[23] who, in his work on the growth of synovial tissue culture, has shown that under low nutritive value of the media, the synovial cells remained the same for about 60 days, provided transplants of the growth to new media were made every 10 days. After 60 days, it was not often possible to prevent transformation into a growth having a fibroblastic character. The cells in their transformation became small and spindle-shaped, with numerous long, sharp, fine processes, and contained smaller and less clearly demarcated nuclei. The highly refractile granules of the synovial cells became smaller and less distinct and disappeared in the next transplant. Generally, the fibroblastic appearance, once formed, tended to remain. In transplants with greater nutritive value media, the fibroblastic changes occurred more readily.

Maximow[24] has also shown that in tissue cultures made of peritoneal exudate, mesothelial cells are transformed into fibroblasts. Key,[25] in his experiments on rabbits, has shown that after performing a complete hemisynovectomy on knees of rabbits, and studying them at regular intervals of two days for the first 22 days, and later six to 18 days apart, up to 104 days after the operation, the joint was again approximately normal, 60 days after the hemisynovectomy. The new synovial membrane was formed *in situ* by the metaplasia of the underlying connective tissue cells, and there was little or no tendency of the surface growths at the edges of the normal synovia to cover the denuded area, as there is in the repair of a defect in an epithelial surface. He believes that the synovial cells are connective tissue cells, slightly specialized by their location on a free connective tissue surface.

This experimental finding is simulated very closely in two of our tumors, in which the clefts are lined by elongated cells having a suggestion of protoplasmic processes with fine fibrils. Murphy,[26] in his work on the ankylosis arthroplasty of the hip joint, has shown the formation of a new synovial space by the interposition of muscle aponeurosis, with the formation of a definite lining membrane.

Similarly, in the malignant form of tumors of the synovial tissue, described by Smith[27] as a synovioma, the tumor is characterized by spaces lined in many instances by low cuboidal epithelial-like cells separated by compact cords of spindle-shaped cells which, in some portions of the tumor mass, are devoid of intercellular substances and fibrils. Mitotic figures are present in both types of cells. He believes that both are derived from a common multipotential cell, since he has shown the synovial lining type and the supporting stromal type with intermediate forms of cells between the two.

In previous observations, made by one of us[28] (A. B. R.), we were impressed in one case by the presence of giant cells in the tumor and their close

topographic relation to old hemorrhagic areas, and the absence, in the second case, of giant cells where recent hemorrhages and old hemorrhagic areas were absent. At that time, the findings led one to consider them giant cells of endothelial origin with a tendency to organize the hematoma. But with the study of additional material in 23 different cases, it was found necessary to withdraw the previous view, and now consider them as part of the ground substance of the tumor mass, for the following reason: In all of the 23 cases, with the exception of one case reviewed in this series, there were giant cells closely related to the type cell, and in seven of these 23 instances, there were found hemorrhage, iron pigment, xanthoma cells or iron pigment-laden histiocytes. Where the iron pigment and xanthoma cells were found, the giant cells were not closely related to these foreign elements but were closely related to areas where the type cell was found. In six cases, there were apparently two types of giant cells, one resembling the foreign body giant cell with peripherally placed pale-stained nuclei closely related to the iron pigment and xanthomatous cells, and the other type having centrally placed nuclei which resembled the nuclei of the type cell and was closely related to the group of tumor cells proper.

This present view agrees with that of Albertini,[14] who considers the giant cells to be derived from mesenchyme and states that they are the same substance as the ground cells, except that their protoplasm has failed to undergo division.

Stewart and Flint[29] have also shown giant cells to be present in the absence of cholesterol deposits. They, however, believe the giant cells to be endothelial in origin.

Other investigators (Fleissig,[30] and Sprenger[1]) believe these cells to be foreign body giant cells, due to the presence of extracellular cholesterin and their ester deposits. Gorog,[5] on the other hand, assumes that the giant cell is part of the ground substance, since, in these tumors, it develops at a remote distance from the cholesterol deposits and in contrast to the true foreign body giant cell which, as a rule, develops immediately around the foreign particle.

Mallory[31] states that at least two different types of giant cells occur in tumors. The true type arises from multiple mitoses and appears in a great variety of rapidly growing tumors, such as the fibrosarcoma or glioblastoma. It does not differ essentially from the other cells of the tumor, except in size. The other, the foreign body giant cell, is formed most commonly in new growths involving bone and occurs in both rapid and slow growing tumors. It is due to endothelial leukocytes invading tumors and fusing to form giant cells. In none of our tumors was there bone involvement, and upon close examination, the nuclear structures of the giant cell in these cases are identical with those found in the type cell.

Although some of the observers, as McWhorter and Weeks,[32] are under the impression that these tumors are due to a systemic disturbance of cholesterol metabolism, as in multiple xanthoma, one should still consider cholesterol deposits as secondary manifestations, undoubtedly due to trauma, since the xanthoma cells are found in close relation to areas of trauma, as in-

dicated by old hemorrhage with liberation of iron pigment and cholesterol by the degenerated red blood cells.

In seven of our cases, where iron pigment was found, xanthoma cells were usually present, and then around a blood vessel, whereas, in the other cases, where no hemorrhage was found, cholesterol deposits, iron pigments and lipophages were absent. In one case, a recent hemorrhage was present with absence of xanthoma cells and cholesterol deposits.

Unfortunately, we were able to obtain only one blood cholesterol determination, and that of a case where the tumor had recurred a second time. The blood cholesterol was 148 mg. per 100 cc., which is quite within normal limits.

Gorog,[5] and Aguilar[17] have also reported normal blood cholesterols in patients suffering from tendon sheath tumors. Furthermore, it has been shown by Stewart,[33] that deposits of cholesterol may occur in various pathologic lesions, one of which is due principally to local tissue changes with no chance for escape of the products of disintegration.

Katsurashima[9] believes that the xanthomatous tissue in question probably developed secondarily in the tumor as a partial manifestation of a constitutionally conditioned hypercholesteremia.

As for the iron pigment, its close topographic relationship to blood vessels indicates that it, like the cholesterol deposits, is derived from degenerating red blood cells. The pigment is readily engulfed by numerous histiocytes.

One more interesting phase is the subject of recurrences. In three cases where there were histories of recurrences, two were not heard from after the second removal of the tumor from the finger, and the other had a second recurrence following a removal 14 months previous. This can easily be explained by the fact that complete extirpation of the tumor was not effected at the second operation. In addition, there was no evidence of metastasis to lymph nodes situated nearby, nor did the patient show constitutional signs of a long standing malignancy.

It seems appropriate, therefore, to consider these growths relatively benign, and if a complete surgical removal is performed, they do not recur. Radical surgery in tumors of this kind is not indicated.

In view of the study of the present material, the giant cells are to be considered as part of the ground substance of the tumor tissue, and this, necessarily, changes the descriptive terminology of the tumor mass from benign tumors to benign giant cell tumors of the tendon sheath.

CONCLUSIONS

(1) Benign giant cell tumors of the tendon sheath are true neoplasms.

(2) Cholesterol and iron pigment deposits are secondary to the tumor growth and are liberated by the degeneration of the red blood cells.

(3) Xanthoma cells are formed only in the presence of iron and cholesterol deposits.

(4) Giant cells are mesenchymal in origin and are part of the ground substance of the benign cell tumor of the tendon sheath.

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